ANNALS OF INTERNAL MEDICINE

Published Monthly by The American College of Physicians

VOL. 53, NO. 1 JULY, 1960

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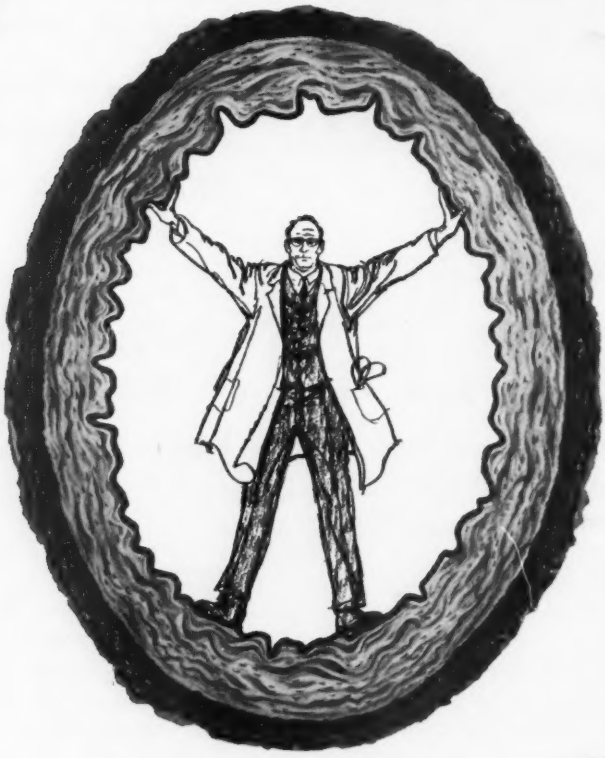
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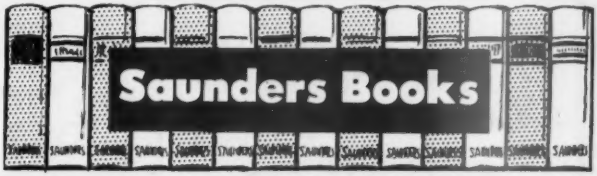
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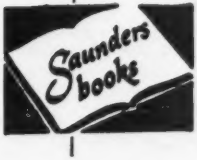
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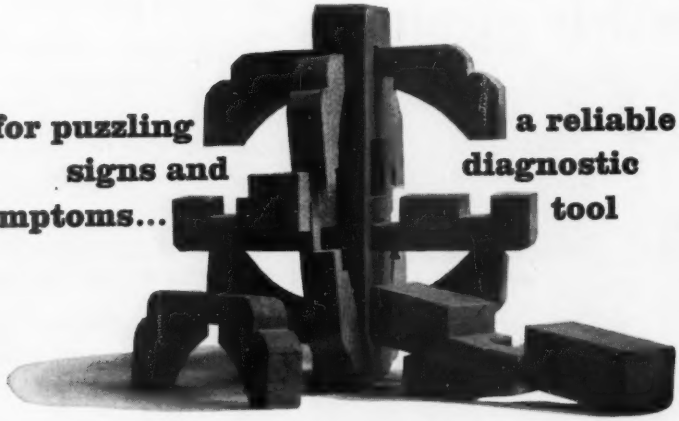
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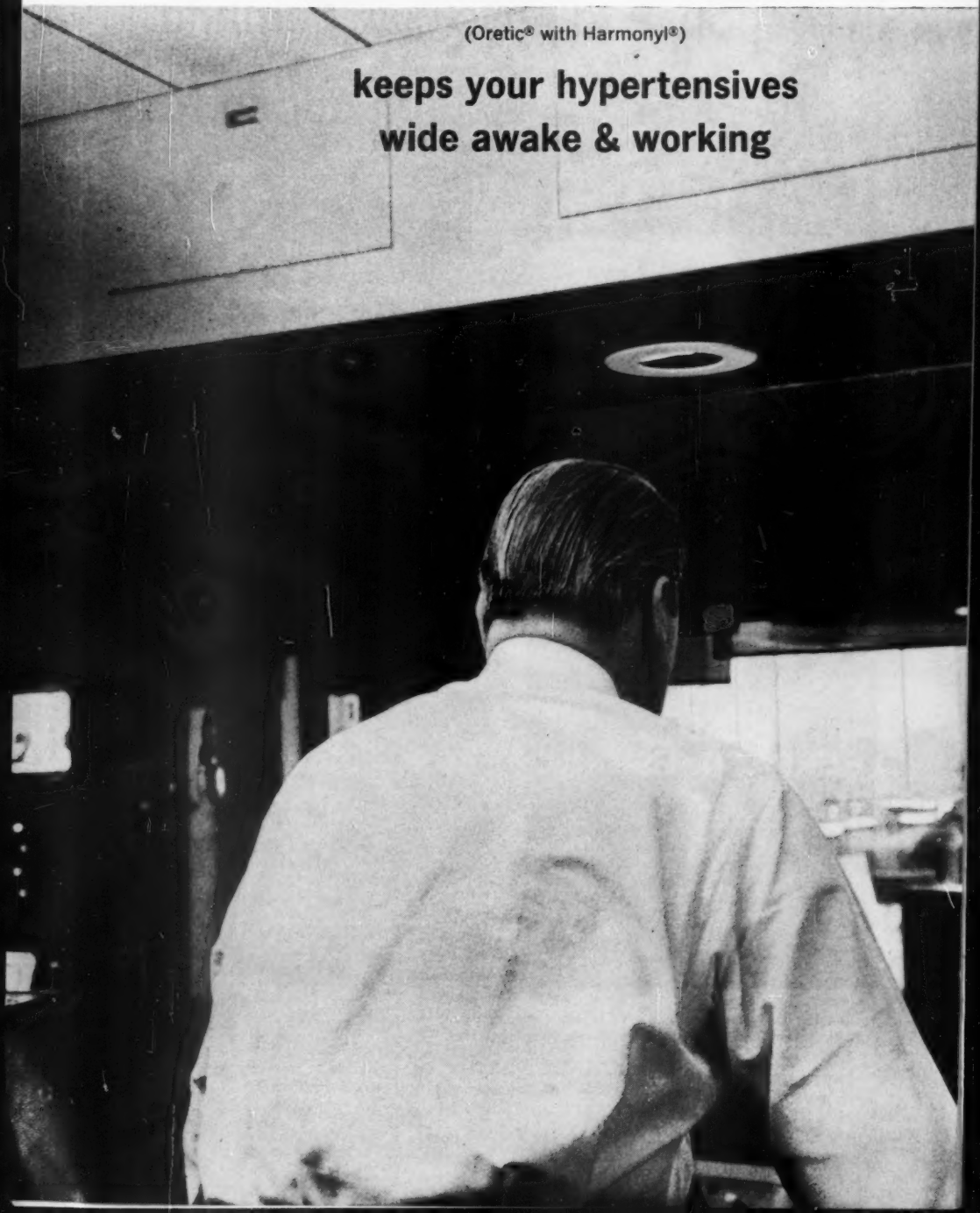
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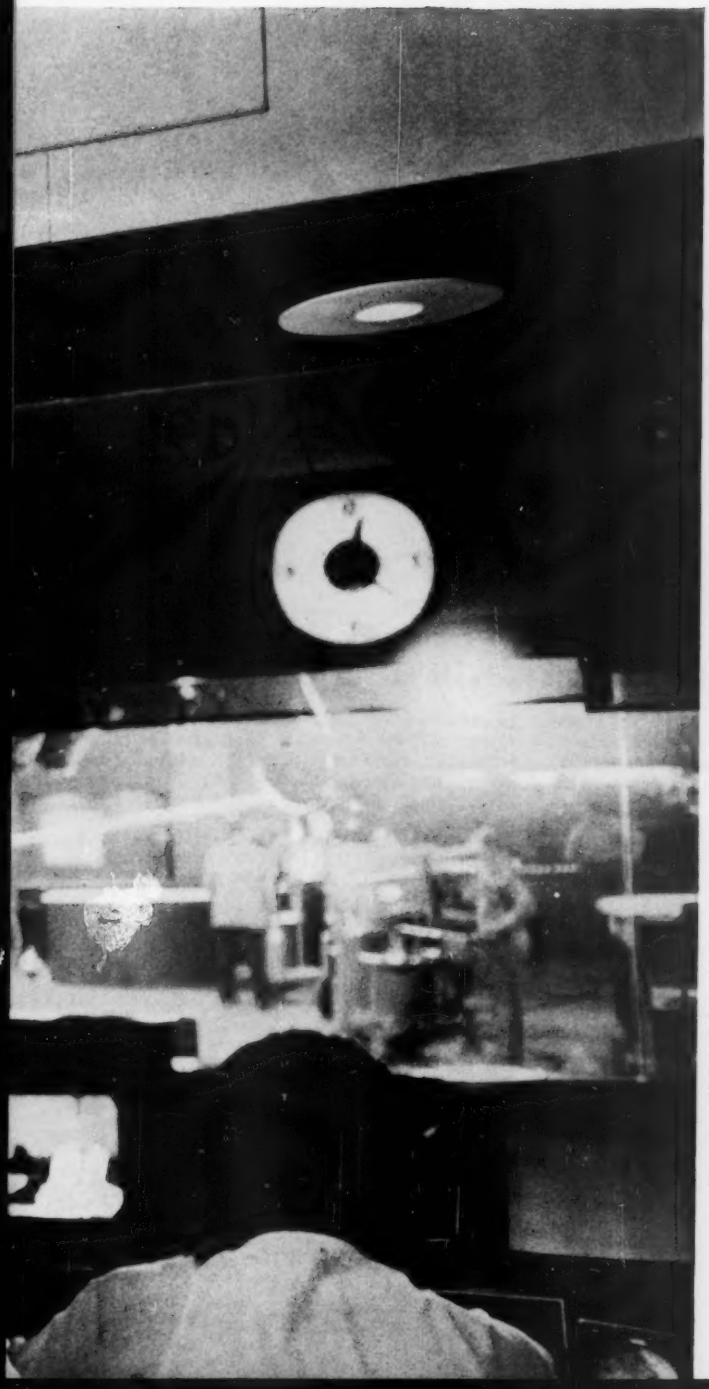
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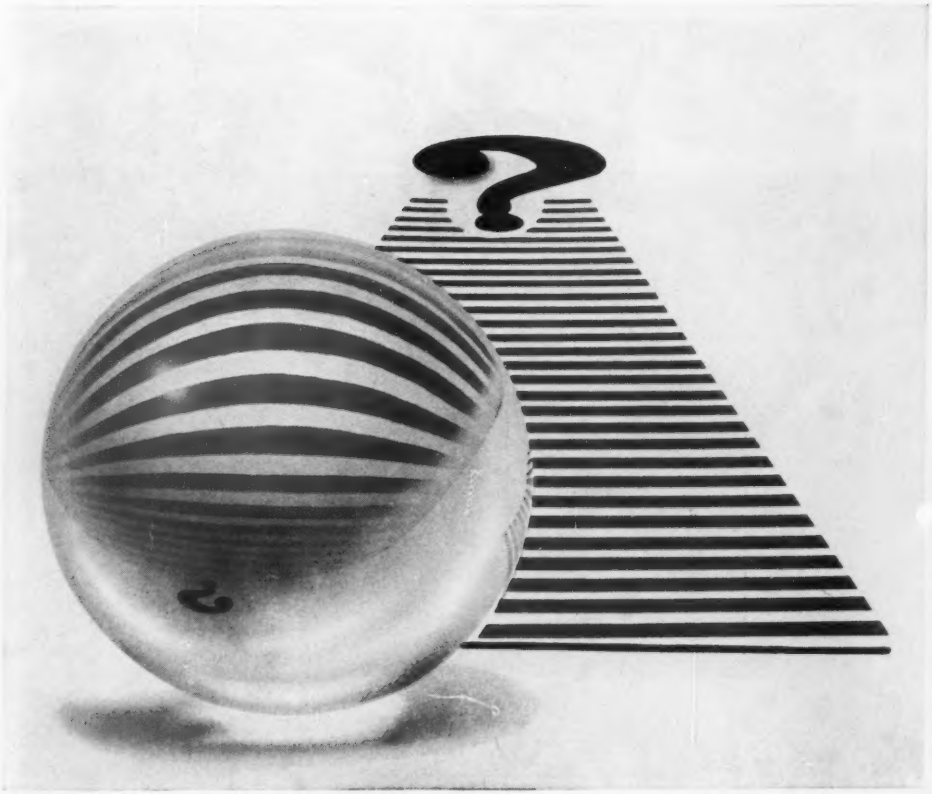
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These are but a few of the many conditions in which flatulence due to intestinal atony is often a complicating and discomforting factor. » Three independent clinical evaluations of patients aged 20 to 80, proved ILOPAN-CHOLINE 90% effective in preventing and relieving retention and distention caused by intestinal atony. » Each ILOPAN-CHOLINE tablet contains 50 mg. d-pantothenyl alcohol — key substance of the coenzyme A molecule required for acetylation, and 25 mg. choline bitartrate — parent substance of acetylcholine essential for peristaltic efficiency.

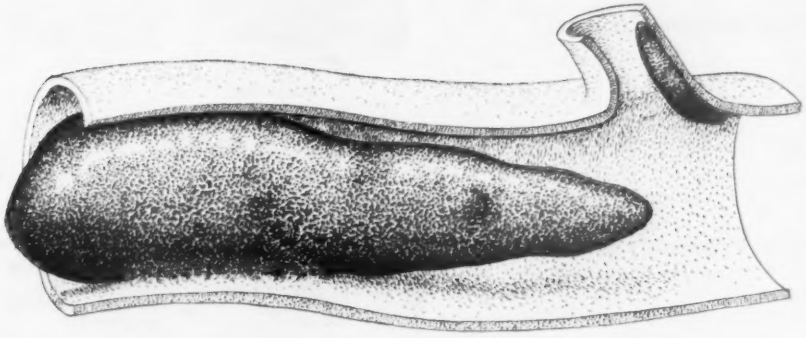
Dosage — 2 tablets, t.i.d. Contraindications — none known. Supplied — bottles of 100 and 500.

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Announcing...a new agent for lysis of

VASCULAR THROMBI



THROMBOLYSIN, supplemented by anticoagulant therapy, can greatly reduce mortality and morbidity in thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi.* Recently formed clots are lysed rapidly, usually in 24 hours.

to lyse thrombi

THROMBOLYSIN.

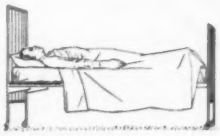
FIBRINOLYSIN, HUMAN



THROMBOLYSIN®

FIBRINOLYSIN, HUMAN

early use greatly reduces morbidity and mortality in thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi

Results of therapy	Bed rest
Effect on intravascular thrombi	 Clot may form permanent obstruction to blood flow. New clots may form.
Effect on pulmonary emboli	 Sudden death from pulmonary embolism is an ever-present hazard. One or more nonfatal pulmonary emboli may result in irreversible lung damage or secondary pneumonia.
Effect on duration of illness and convalescence	 Weeks of hospitalization or bed rest at home are commonly required in the management of thrombophlebitis, phlebothrombosis, pulmonary embolism, and arterial thrombosis.
Frequency and severity of postphlebitic syndrome	 Chronic leg swelling, severe secondary varicose veins, and leg ulcers are common sequelae.



MSD

Anticoagulant + Bed rest	THROMBOLYSIN + Anticoagulant + Bed rest
 Anticoagulants cannot remove formed clot. However, they help prevent its extension and minimize formation of new clots.	 Recently formed intravascular clots are lysed and the formation of new clots is inhibited. Circulation is restored and maintained, with rapid symptomatic relief.
 The careful use of anticoagulants reduces the occurrence of pulmonary emboli.	 The incidence and severity of pulmonary emboli are greatly reduced since THROMBOLYSIN acts to remove thrombi before they can become emboli.
 Thromboembolic illness and convalescence are shortened.	 A striking reduction is observed in the duration of hospital stay, bed rest, and convalescence.
 The incidence and severity of the postphlebitic syndrome are reduced.	 Postphlebitic complications are prevented or greatly minimized.



What is THROMBOLYSIN?

THROMBOLYSIN is Fibrinolysin, Human. It is prepared by activating the profibrinolysin-rich Fraction III – 3 of pooled human plasma with highly-purified streptokinase and then lyophilizing it. THROMBOLYSIN helps restore the natural equilibrium between clot formation and clot lysis, thereby enhancing the ability of the blood to maintain normal flow.

In What Conditions is it Indicated?

THROMBOLYSIN is indicated in thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi.

*(NOTE: *Successful lysis of thrombi of major cerebral vessels has been reported. However, additional experience is required to define the indications and contraindications of therapy in such patients. THROMBOLYSIN has also been administered to patients with acute myocardial infarction, but the scope of this work is still too limited to permit conclusions about its safety or benefit.*)

When Should Therapy be Initiated?

Treatment with THROMBOLYSIN should be started as soon as possible after a thrombus has formed. Blood clots begin to organize shortly after formation and may become encased in a layer of endothelial cells, making them resistant to the action of THROMBOLYSIN. Usually, more rapid lysis can be expected to take place when treatment is initiated within five days after a thrombus has formed; however, in some cases successful lysis has been accomplished when treatment was not initiated for several weeks after thrombus formation.

Can THROMBOLYSIN be Given to Patients Being Treated with Anticoagulants?

Yes. Patients who have been on anticoagulant therapy can be expected to improve when THROMBOLYSIN is added to their program of treatment.

Does THROMBOLYSIN Increase the Incidence of Embolism?

Clinical studies indicate that it does not. In fact, if any evidence of embolization should appear, it is important to continue THROMBOLYSIN until symptoms have disappeared.

What is the Dosage?

The dosage most frequently used by investigators has been 4 vials (200,000 MSD units) per day by intravenous infusion. This is usually administered by giving 1 vial per hour for 4 consecutive hours. Alternatively, 1 vial (50,000 MSD units) per hour may be given for 2 consecutive hours and repeated in 3 to 6 hours. The dosage range is 1 vial (50,000 MSD units) to 2 vials (100,000 MSD units) an hour by intravenous drip, for 1 to 6 hours, depending on the nature of the clot and the response

Vascular thrombi
can now be
treated rapidly
by a new agent

THRO

For additional information, see package circular or write to Professional Services, Merck Sharp & Dohme, West Point, Pa.



of the patient. Most patients respond in one day; those who do not may require additional doses for three or four successive days.

Patients not under active treatment with anticoagulants at the time of the thromboembolic episode:

New clot formation is unlikely to occur during the administration of THROMBOLYSIN, so that anticoagulants may be unnecessary in this period. However, the fibrinolytic activity of THROMBOLYSIN persists only 3 to 4 hours after cessation of infusion; in patients subject to thrombosis, provision should be made to provide adequate therapeutic anticoagulant effect at this time.

Patients under active treatment with anticoagulants:

Within recommended dosages, THROMBOLYSIN produces only minor alterations in the clotting mechanism: the prothrombin time is generally increased by only a few seconds, the Lee-White clotting time by only 1 to 4 minutes, and the fibrinogen levels generally decrease by about 30 percent of control values. In themselves, these alterations are probably of no clinical significance. In patients on concurrent anticoagulant therapy in whom the clotting mechanism is depressed to midtherapeutic levels, the small additional depression due to THROMBOLYSIN should produce no added danger; however, the addition of THROMBOLYSIN may be hazardous when the therapeutic anticoagulant level already threatens to exceed safe limits.

What Other Precautions are Necessary?

THROMBOLYSIN is contraindicated in the presence of a hemorrhagic diathesis or hypofibrinogenemia. Fibrinolytic activity usually increases spontaneously for a short period after anesthesia or surgery. Therefore, THROMBOLYSIN should be used with caution because lysis of the clots at the operative site may occur.

Bleeding from open wounds or recent operative sites can occur during therapy. Usually this has been observed only in patients receiving both an anticoagulant and THROMBOLYSIN. In such cases, the bleeding was controlled by the use of plasma or whole blood transfusions. A specific antagonist to the anticoagulant may also be used.

What Side Effects May Occur?

Febrile reactions may occur, but these are rarely severe. When they do occur, the temperature usually rises rapidly to a peak, then returns to normal within 24 hours. In some patients, a rise in temperature above 1.5 to 2 degrees F. is accompanied by chills, nausea, vomiting, dizziness, headache, muscle pain, back pain, tachycardia, or hypotension.

How is it Supplied? 100-cc. vials containing 50,000 MSD units.

to lyse thrombi

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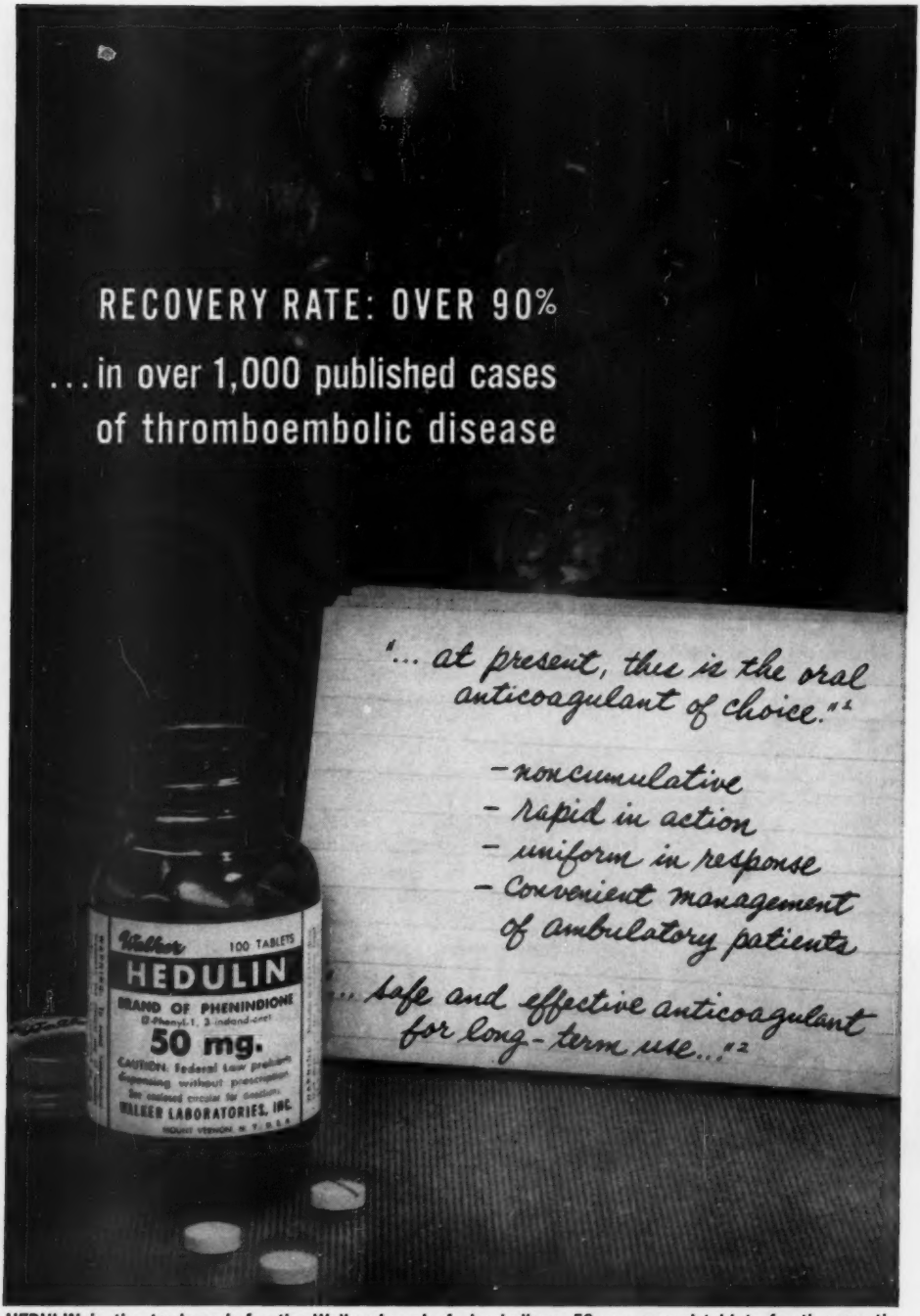
FIBRINOLYSIN, HUMAN

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

THROMBOLYSIN IS A TRADEMARK OF MERCK & CO., INC.



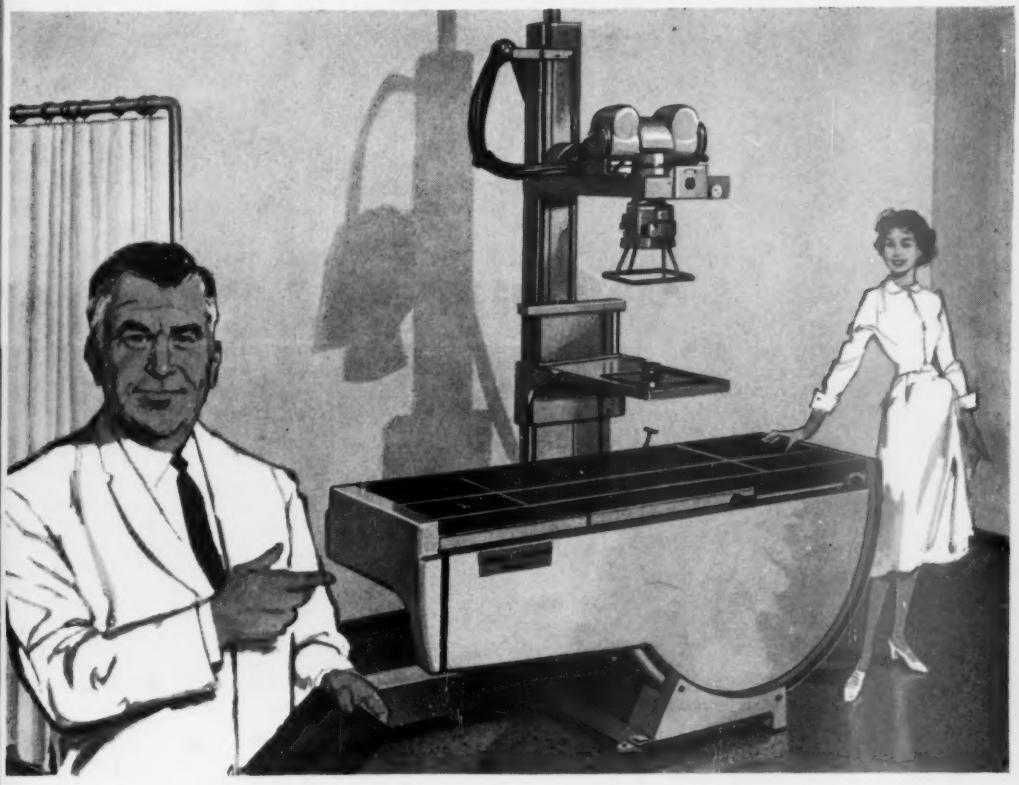
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HEDULIN is the trademark for the Walker brand of phenindione. 50 mg. scored tablets for therapeutic use; 20 mg. scored tablets for prophylactic use. Bottles of 100 and 1,000. For more detailed information and a clinical trial supply of Hedulin, write to Walker Laboratories, Inc., Mount Vernon, N. Y.

1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

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EQUANITRATE helps control pain and accompanying anxiety in angina pectoris. It reduces the number and severity of attacks, increases exercise tolerance, and lessens nitroglycerin dependence.

A recent double-blind study† comparing meprobamate, a placebo, PETN, and EQUANITRATE states: "The best results . . . in both clinical and electrocardiographic response, were observed with a combination of meprobamate and pentaerythritol tetranitrate [EQUANITRATE]. . . ."

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†Russek, H.I.: Am. J. Cardiol. *3*:547 (April) 1959. *Trademark

Supplied: **EQUANITRATE 10** (200 mg. meprobamate, 10 mg. pentaerythritol tetranitrate), white oval tablets, vials of 50. **EQUANITRATE 20** (200 mg. meprobamate, 20 mg. pentaerythritol tetranitrate), yellow oval tablets, vials of 50.



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particularly suited for arthritic patients

Combining the antacid MAALOX® with aspirin increases both absorption and utilization of the salicylate. As a result, ASCRIPTIN acts twice as fast as plain aspirin and analgesic action lasts much longer due to maintenance of higher plasma salicylate levels.

Gastric irritation seldom occurs with ASCRIPTIN even if large doses are given for long periods.

Of particular value in arthritis and rheumatic disease, ASCRIPTIN is an excellent salicylate for routine use.

Formula: Acetylsalicylic acid 0.30 Gm., MAALOX (magnesium-aluminum hydroxides) 0.15 Gm. Offered: Bottles of 100 and 500.

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hearing improved...

tinnitus
and vertigo
relieved in
circulatory disturbances
of the inner ear[1]



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effective in twice as many patients

In patients with disturbances of the inner ear— impaired hearing, tinnitus or vertigo — Arlidin produced remission of their chief complaint in over 50% of cases. Rubin and Anderson state "we were very much encouraged, inasmuch as no other vasodilator that we have used has ever achieved more than a 25 per cent response."

"significant hearing improvement"

was obtained in 32 of the 75 patients studied.

rationale: The clinicians note that impairment in hearing, disturbance in balance, and tinnitus involving the inner ear "may be explained on the basis of labyrinthine artery insufficiency" due to spasm or obstruction of the vessels. Arlidin was found to be "superior to all other vasodilating measures" in increasing blood flow through these vessels and in allaying spasm.

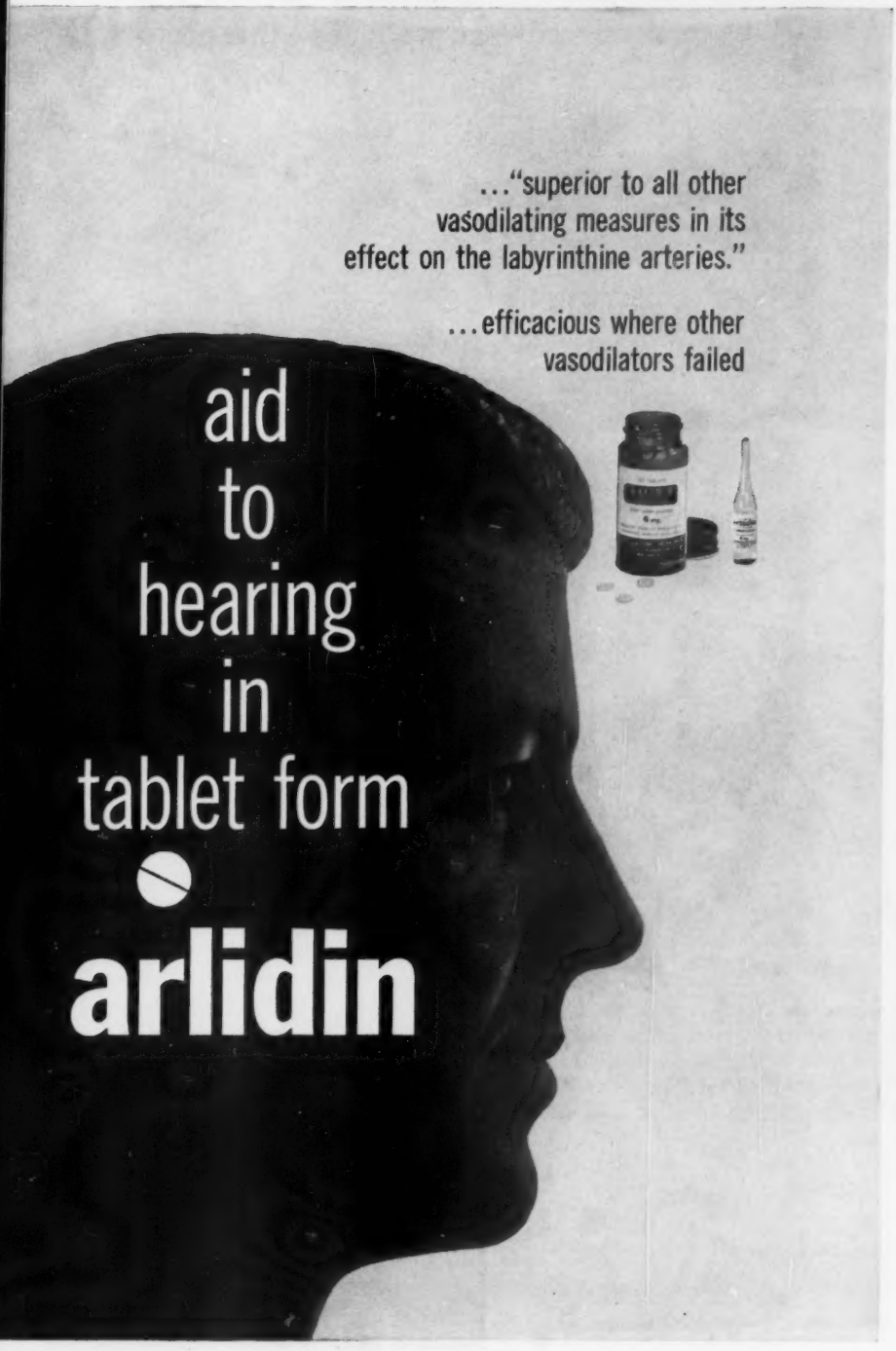
Arlidin is available in 6 mg. scored tablets, and 5 mg. per cc. parenteral solution. See PDR for dosage and packaging.

Protected by U. S. Patent Numbers: 2,661,372 and 2,661,373

1. Rubin, W., and Anderson, J. R.: Angiology 9:256, 1958.

u. s. vitamin & pharmaceutical corporation

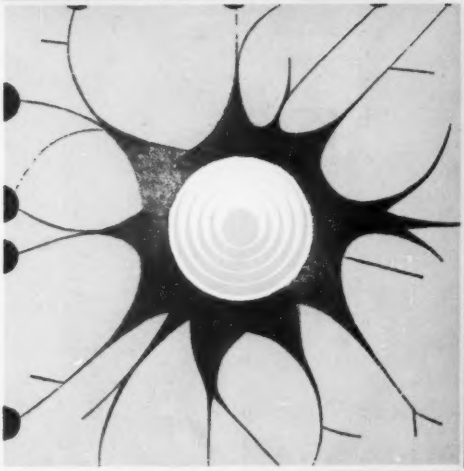
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..."superior to all other
vasodilating measures in its
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whenever depression complicates the picture

Tofrānil®
brand of imipramine HCl



hastens recovery

Geigy

In many seemingly mild physical disorders an element of depression plays an insidious etiologic or complicating role.

Because of its efficacy as an antidepressant, coupled with its simplicity of usage, Tofrānil is admirably adapted to use in the home or office in these milder "depression-complicated" cases.

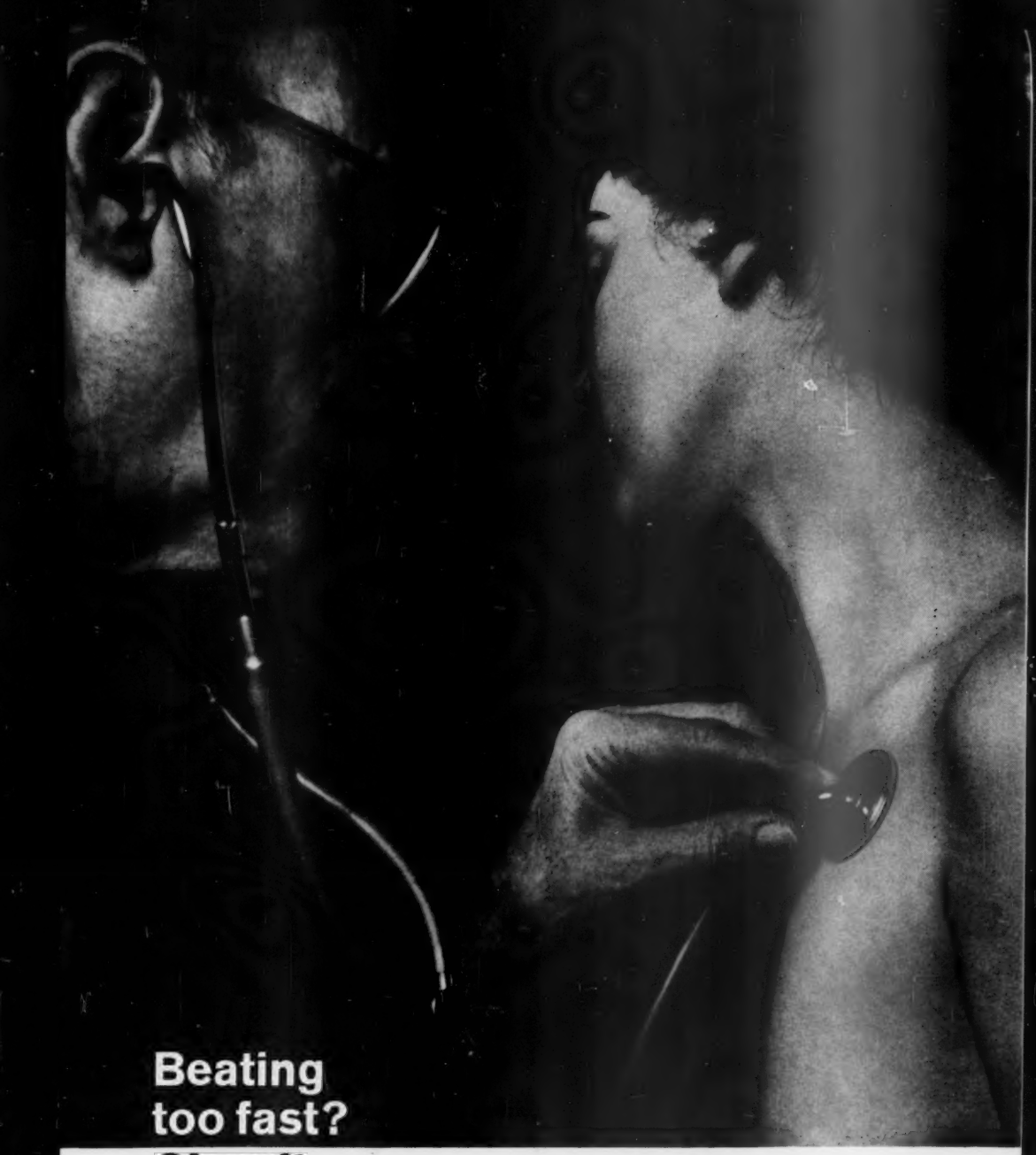
It is always wise to recognize that depression may be an underlying factor... that Tofrānil may speed recovery in "hypochondriasis"; in convalescence when recovery is inexplicably prolonged; in chronic illness with dejection; in the menopausal patient whose emotional disturbances resist hormone therapy, and in many other comparable situations in which latent depression may play a part.

Detailed Literature Available on Request.

Tofrānil®, brand of imipramine hydrochloride, tablets of 25 mg. Ampuls for intramuscular administration, 25 mg. in 2 cc. of solution.

Geigy, Ardsley, New York

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Beating too fast?

Slow it down with SERPASIL®

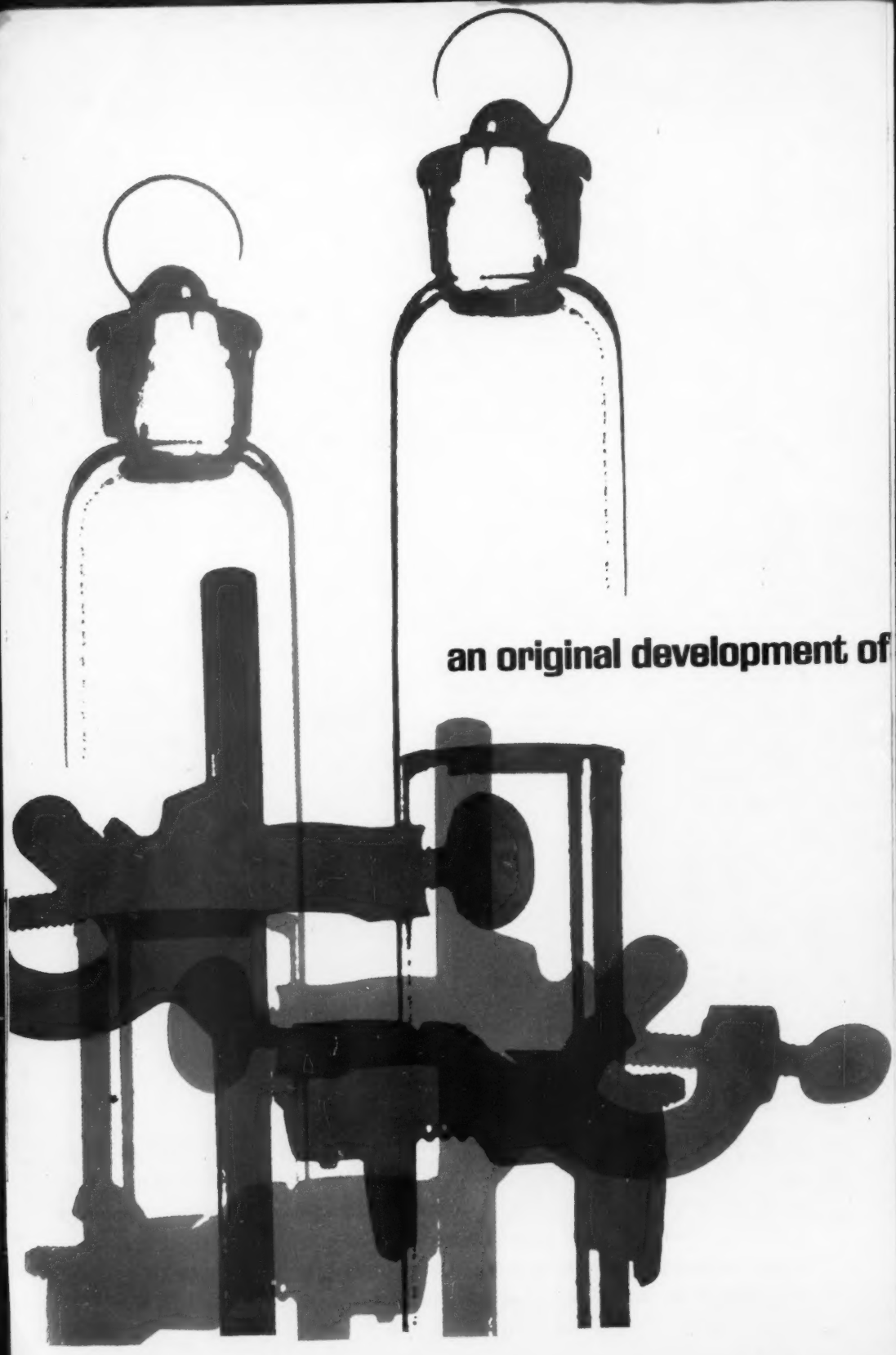
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Serpasil has proved effective as a heart-slowing agent in the following conditions: mitral disease; myocardial infarction; cardiac arrhythmias; neurocirculatory asthenia; thyroid toxicosis; excitement and effort syndromes; cardiac neurosis; congestive failure. Serpasil should be used with caution in patients receiving digitalis and quinidine. It is not indicated in cases of aortic insufficiency.

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successor in specificity: relieves anxiety, agitation and tension, and liberates the patient from destructive fears.

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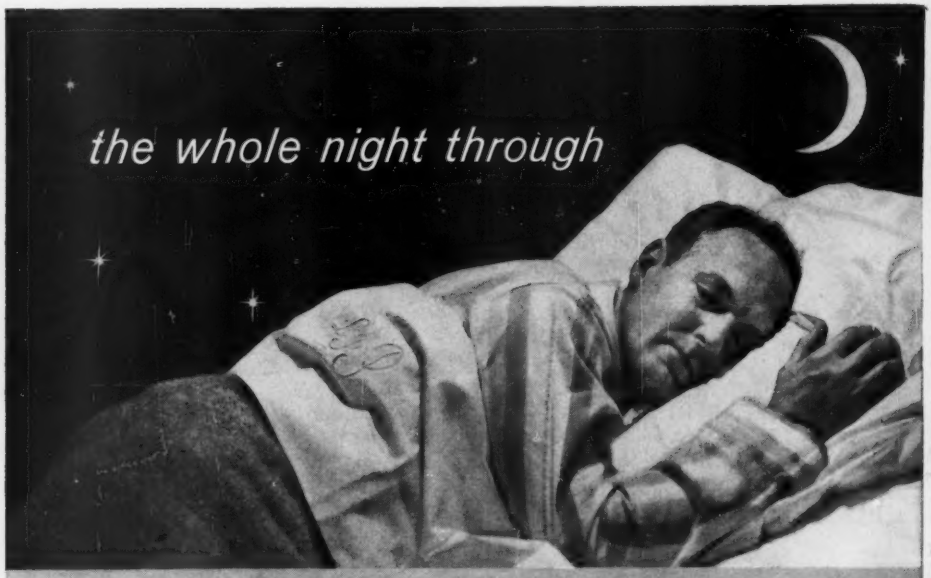
successor in effect: acts with remarkable promptness; preserves full mental acuity; produces a feeling of well-being, increased drive and a broadening of interest.

Consult literature for dosage instructions.

Published reports on Librium: 1. T. H. Harris, *Dis. Nerv. System*, *21*:(Suppl.), 3, 1960. 2. L. O. Randall, *ibid.*, p. 7. 3. J. M. Tobin, I. F. Bird and D. E. Boyle, *ibid.*, p. 11. 4. H. A. Bowes, *ibid.*, p. 20. 5. J. Kinross-Wright, I. M. Cohen and J. A. Knight, *ibid.*, p. 23. 6. H. H. Farb, *ibid.*, p. 27. 7. C. Breitner, *ibid.*, p. 31. 8. I. M. Cohen, Discussant, *ibid.*, p. 35. 9. G. A. Constant, *ibid.*, p. 37. 10. L. J. Thomas, *ibid.*, p. 40. 11. R. C. V. Robinson, *ibid.*, p. 43. 12. S. C. Kaim and I. N. Rosenstein, *ibid.*, p. 46. 13. H. E. Ticktin and J. D. Schultz, *ibid.*, p. 49. 14. J. N. Sussex, *ibid.*, p. 53. 15. I. N. Rosenstein, *ibid.*, p. 57. 16. D. C. English, *Curr. Therap. Res.*, *2*:88, 1960. 17. T. H. Harris, *J.A.M.A.*, *172*:1162, 1960. 18. G. L. Usdin, *J. Louisiana M. Soc.*, *112*:142, 1960. 19. I. N. Rosenstein and C. W. Silverblatt, paper read at Pan American Medical Association, 35th Anniversary Congress, Mexico City, Mexico, May 2-11, 1960. 20. K. Rickels, *ibid.* 21. N. Toll, *Dis. Nerv. System*, *21*:264, 1960.

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Quinidine Gluconate (5 gr.)

maintains normal sinus rhythm
in cardiac arrhythmias

Dosage with Quinaglute Dura-Tab S.M. is "relatively simple."[1] One dose q. 12 h. maintains effective, uniform quinidine blood levels around the clock, all night, all day. There are no valleys in blood concentration where arrhythmias tend to recur.

Better tolerated — because quinidine gluconate is ten times as soluble as quinidine sulfate—and easier on the g.i. tract. And because only a fraction of the daily dose of Quinaglute Dura-Tab S.M. is released in the stomach.

A quinidine of choice in control of atrial fibrillation, flutter, premature contraction, auricular tachycardia.[1-4] Bottles of 30, 100 and 250.

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Also available: INJECTABLE QUINAGLUTE
*U.S. Patent 2,895,881

1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Arch. Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.
3. Finkelstein, D.: Penn. Med. J. 61:1216, 1958.
4. Bellet, S.: Amer. J. Cardiology 4:268, 1959.

REFER TO PDR
PAGE 893

THE WM. S. MERRELL COMPANY
announces the availability of

MER/29

(brand of triparanol)

... the first cholesterol-lowering agent to inhibit the formation of excess cholesterol within the body, reducing both serum and tissue cholesterol levels.

... no demonstrable interference with other vital biochemical processes reported to date.

... convenient dosage: one 250 mg. capsule daily

... toleration and absence of toxicity established by 2 years of clinical investigation.

The following pages report the clinical findings of therapy with MER/29 among patients with hypercholesterolemia and conditions thought to be associated with it, such as

coronary artery disease (angina pectoris, postmyocardial infarction)

generalized atherosclerosis

THE FACTS ABOUT MER/29[1-41]

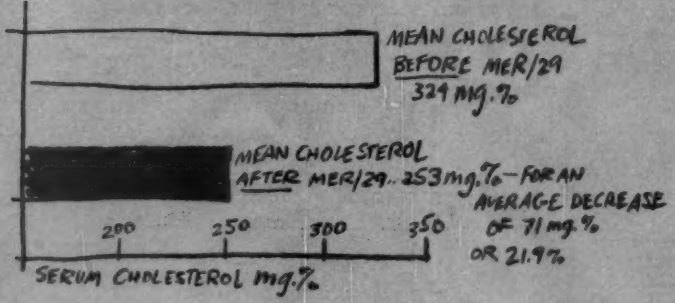
Fundamental differences between MER/29 and other cholesterol-lowering substances

Cholesterol produced within the body by biosynthesis is about three times as great in amount as that obtained from diet. Before MER/29, no practical method of modifying total body cholesterol production was known. Those measures used to lower cholesterol (unsaturated fatty acids or other dietary measures, vitamins, plant sterols, hormones, etc.) succeeded only in modifying exogenous sources of cholesterol or accelerating its metabolism.

MER/29 is fundamentally different, since it inhibits cholesterol biosynthesis. Thus, MER/29 offers for the first time a method of controlling total body cholesterol content.

MER/29 reduces serum cholesterol in 89% of patients, with or without dietary restrictions. Radioisotope studies indicate reduction of tissue cholesterol as well.[4, 5, 7, 30, 31, 34]

High cholesterol levels are generally considered those above 250 mg.%. Here is a tabular summary of preliminary data on MER/29 therapy in 463 patients with hypercholesterolemia (over 250 mg.%).



Clinical studies show that cholesterol reduction usually begins within two weeks. Maximum effect is achieved in five to eight weeks, and is usually maintained as long as therapy is continued. The studies of Hollander, Chobanian and Wilkins and those of Oaks, Lisan and Moyer showed that cholesterol levels were lowered by MER/29 therapy, irrespective of diet.

Reduction of total body "miscible pool" of cholesterol has been confirmed by radioisotope studies. Hollander and Chobanian, for example, found that the apparent miscible pool of cholesterol was reduced from 184 Gm. in the control period to 100 Gm. during MER/29 administration.

Studies in animals on MER/29 have shown the following tissue changes: erythrocyte cholesterol levels reduced 40%; plasma cholesterol reduced 62%; liver reduced 40%; skeletal muscle reduced 27%; lung reduced 33%; aorta reduced 21%. Significantly, brain and adipose tissue remained unaffected during the period of observation.

Safety and toxicity studies[5, 7, 10, 12, 17, 19, 21-24, 30, 32-34]

MER/29 is well tolerated. In a recent analysis of 576 individual case reports, 165 had been treated with MER/29 for continuous periods in excess of a year. A number had received two to four times the daily recommended dose for as long as 14 months. Side effects were seldom seen, and the incidence of those reported (nausea, dermatitis) usually was correlated with dosages greater than those now recommended.

In no case has there been clinical indication of toxic effects on the function of any vital organ or system. It should be noted that excretion of MER/29 or its metabolites may produce a false positive reaction for albuminuria.

THE FACTS ABOUT MER/29

Clinical observations of MER/29 in atherosclerosis[5, 7, 10, 12, 17-19, 21, 23-25, 28-34, 41]

The lowering of high cholesterol levels is regarded by many as a desirable clinical objective. Moreover, a substantial body of medical opinion implicates elevated cholesterol as a contributor to coronary artery disease and generalized atherosclerosis. Since MER/29 lowers total body cholesterol, can it modify atherosclerotic conditions? While the ultimate answer must await the results of long-term clinical experience, preliminary observations were reported at...

The MER/29 Conference at Princeton

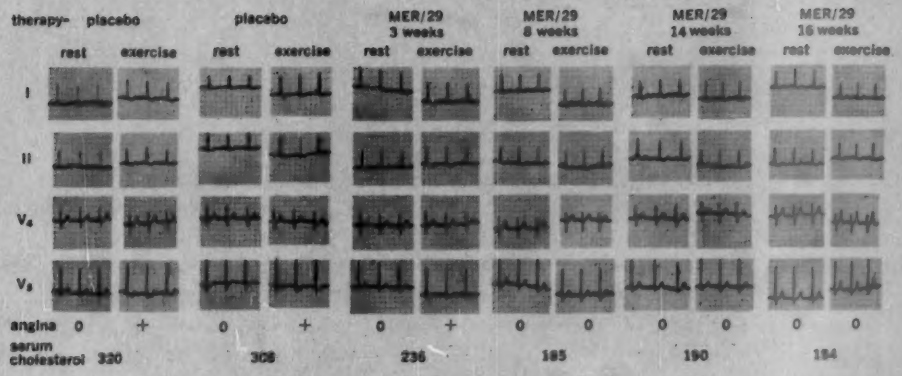
To help find the answer, 18 leading research teams met to discuss the relationship of MER/29 to cholesterol metabolism and atherosclerosis. The conference, moderated by Dr. Irving S. Wright, and summarized by Dr. Konrad E. Bloch, Dr. Robert W. Wilkins, and Dr. Irvine H. Page, was held last December at Princeton, New Jersey.

(The complete transcript of this conference is published as a supplement to the May, 1960, issue of Progress in Cardiovascular Diseases.)

Objective findings

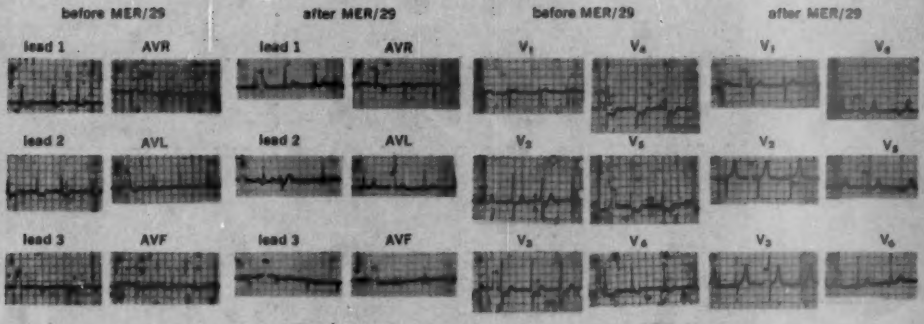
The team of Dr. William Hollander, Dr. Aram V. Chobanian, and Dr. Robert W. Wilkins at Massachusetts Memorial Hospitals presented Fig. 1. It indicates a reversal of exercise-precipitated ECG abnormalities in a patient with angina pectoris during four months of MER/29 therapy. In all, they reported that three of nine patients showed reversal of exercise-induced ECG abnormalities after three months of MER/29 therapy.

Figure 1



Dr. Philip Lisan of Dr. John H. Moyer's group at Hahnemann Hospital presented Fig. 2. It also indicates reversal or ECG abnormalities in a patient with angina pectoris.

Figure 2



Dr. A. C. Corcoran of St. Vincent Charity Hospital, Cleveland, and Dr. Arthur Ruskin of University of Texas reported similar objective findings. Many of these investigators noted that patients offered subjective evidence that they were experiencing a feeling of better health on MER/29 therapy, and that nitroglycerine dependence was diminishing.

Negative data were presented by Dr. Henry I. Russek of Staten Island, N. Y. He reported a study of exercise-electrocardiographic tests in 14 selected

subjects on MER/29. None of these patients had shown more than transient improvement in exercise tolerance after 3 months of treatment. It should perhaps be noted that this group of angina pectoris patients was a select group, having complained of symptoms for long periods of time.

Subjective findings

Dr. Meyer H. Halperin of Lynn, Massachusetts, reported a series of 18 patients with angina pectoris. Nine of this group obtained unequivocal subjective relief of symptoms after various periods of therapy with MER/29. An analysis of the duration of symptomatology in these patients indicated that response occurred more frequently when the ischemic heart disease had been present for shorter periods. Specifically, those who responded had had the condition for an average of 2.9 years, while the average time for those who did not respond was 5.2 years.

This study suggests that improvement in angina pectoris, when it occurs, may best be expected in those patients in whom the symptoms have been present for shorter periods of time. Additional experience will be required to determine whether long-term therapy can reverse long-standing symptomatology.

Dr. William B. Kountz of the Washington University School of Medicine, St. Louis, reported a group of 79 patients with varying degrees of hypertension, angina pectoris, diabetes, atherosclerosis or myocardial infarction. "Clinical improvement was observed and was also reported to us by patients. In some instances the anginal pain improved very much."

Similar subjective findings were also reported by

Dr. Corcoran, eight of whose nine patients noted a feeling of better health, while five demonstrated electrocardiographic improvement on MER/29. In three of these patients, nitroglycerine requirements were dramatically reduced.

IN SUMMARY ... MER/29 does consistently lower total body cholesterol by inhibition of endogenous cholesterol formation. Some patients with coronary artery disease, while on MER/29, have experienced concurrent clinical benefits such as reduction in frequency and severity of anginal attacks, reduction in nitroglycerine dependence, reversal of ECG abnormalities both at rest and following exercise-induced changes, and a sense of improved health and well-being.

The explanation of these clinical benefits is as yet unknown; however, several hypotheses have been advanced. One group speculates that MER/29 "may actually improve the adequacy of coronary circulation." Another investigator suggests that MER/29 exerts a vasodilating action, though pharmacologically MER/29 produces only transient vasodilating effects. Whatever the explanation, observation of these benefits among certain patients has awakened mounting interest in MER/29 as an important new agent in the management of patients with hypercholesterolemia and atherosclerosis.

MER/29 may be given to your patients with hypercholesterolemia and conditions thought to be associated with elevated cholesterol levels, including coronary artery disease (angina pectoris and postmyocardial infarction) and generalized atherosclerosis.

THE WM. S. MERRELL COMPANY
announces the availability of

MER/29

(brand of triparanol)

... the first cholesterol-lowering agent to inhibit the formation of excess cholesterol within the body, reducing both serum and tissue cholesterol levels.

Indications: May be used for patients with hypercholesterolemia and conditions thought to be associated with elevated cholesterol levels, including coronary artery disease (angina pectoris and postmyocardial infarction) and generalized atherosclerosis.

Caution: MER/29 is a new drug which inhibits cholesterol biosynthesis in the body. Since cholesterol plays an important role in the development of the fetus, the drug should not be administered during pregnancy.

Hypercholesterolemia and its associated conditions may require MER/29 therapy over a long period. MER/29 has been shown to be entirely safe in the periods the drug has been studied, but long-term or lifetime effects are unknown. Periodic examination of patients on long-term MER/29 therapy is therefore necessary. While clinical liver damage has not been encountered, periodic liver function tests may be desirable until more long-term safety data are available.

Note: The specific site of action of MER/29 is now known to be between desmosterol (reported to be the last precursor in the synthesis path) and cholesterol. Although greater than normal quantities of desmosterol can be qualitatively shown in the livers and blood of animals and the blood of human beings treated with MER/29, reduction of total sterols suggests little, if any, accumulation. The significance of the presence of this substance is unknown and speculative.

Compatibility with other cardiovascular therapies: MER/29 is not to be considered a substitute for measures ordinarily employed to control anxiety, hypertension, obesity, and other conditions associated with cardiovascular disorders. However, MER/29 is compatible with measures used in these disorders, including anticoagulants, nitroglycerine, and PETN.

Dosage: One capsule daily, before breakfast. Each capsule contains 250 mg. triparanol.

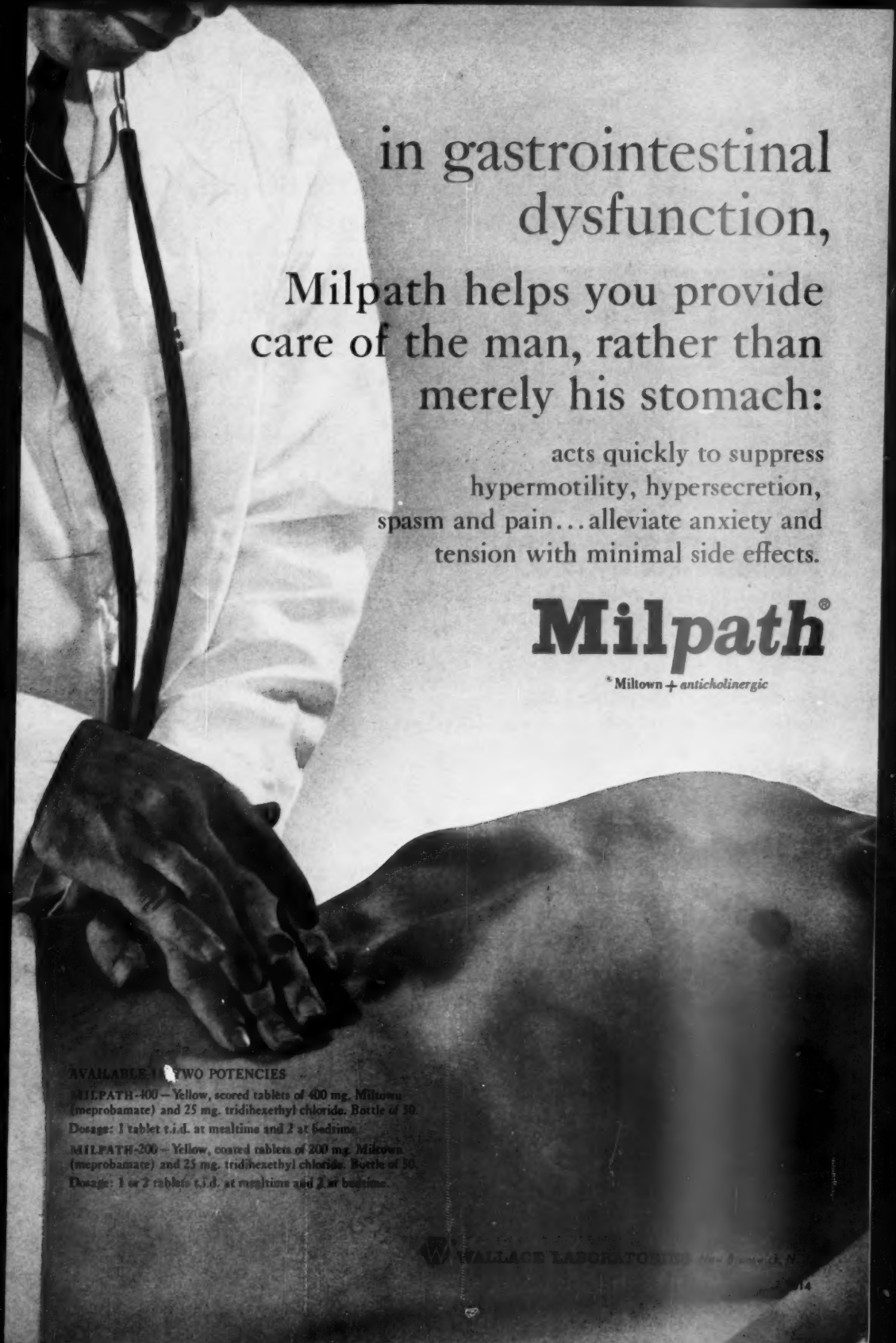
Supplied: In bottles of 30 pearl gray capsules.

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WARFARIN POTASSIUM, PURDUE FREDERICK

THE BEST ORAL ANTICOAGULANT BECOMES EVEN BETTER—AND LESS COSTLY

THE FIRST POTASSIUM SALT OF WARFARIN

- Retains all the therapeutic advantages of earlier Warfarin molecules, but eliminates the sodium ion.
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CHYMORAL PRODUCED GOOD TO EXCELLENT RESULTS IN 77% OF CASES . . . WITH NO EVIDENCE OF TOXICITY OR SIDE EFFECTS[1-4]

condition	no. of cases	excellent/good	fair	no response
sinusitis and tonsillitis	18	14	2	2
asthma with or without bronchitis, emphysema	54	44	7	3
tracheo-bronchitis, bronchitis, bronchiectasis	31	21	7	3
TOTAL	103	79	16	8

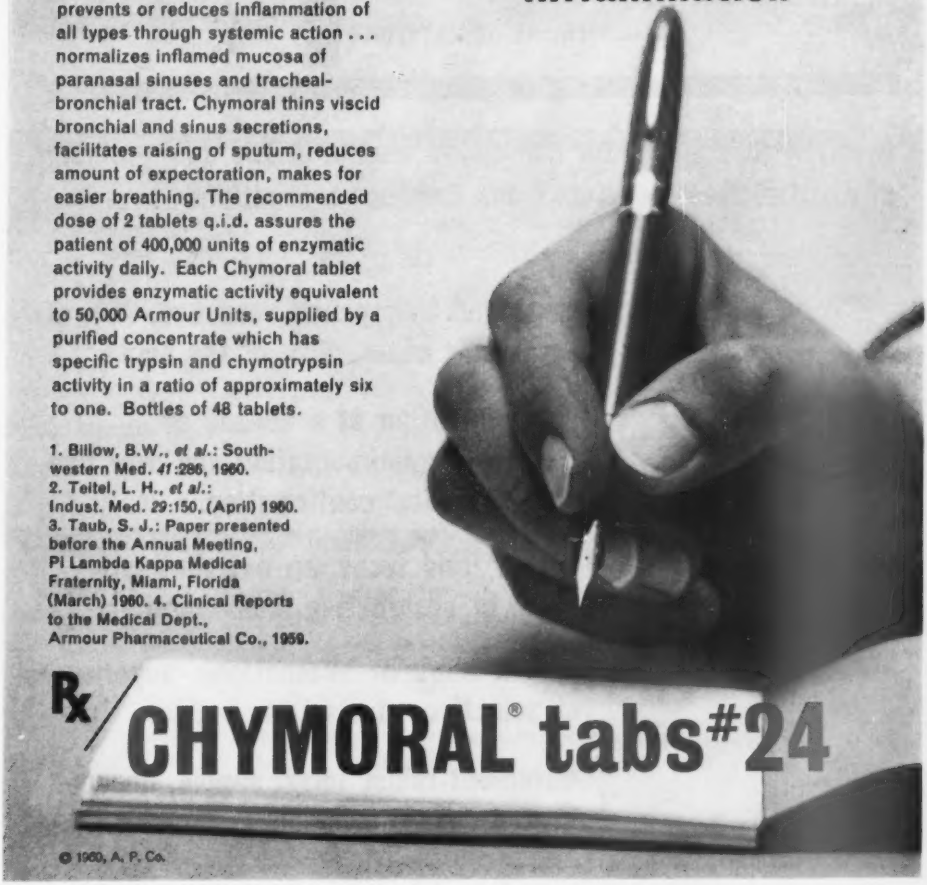
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Chymoral cuts healing time where inflammatory complications prolong the clinical course

Chymoral, *a new ORAL anti-inflammatory enzyme tablet* formulated especially for intestinal absorption, prevents or reduces inflammation of all types through systemic action . . . normalizes inflamed mucosa of paranasal sinuses and tracheal-bronchial tract. Chymoral thins viscid bronchial and sinus secretions, facilitates raising of sputum, reduces amount of expectoration, makes for easier breathing. The recommended dose of 2 tablets q.i.d. assures the patient of 400,000 units of enzymatic activity daily. Each Chymoral tablet provides enzymatic activity equivalent to 50,000 Armour Units, supplied by a purified concentrate which has specific trypsin and chymotrypsin activity in a ratio of approximately six to one. Bottles of 48 tablets.

1. Billow, B.W., *et al.*: Southwestern Med. *41*:286, 1960. 2. Teitel, L. H., *et al.*: Indust. Med. *29*:150, (April) 1960. 3. Taub, S. J.: Paper presented before the Annual Meeting, Pi Lambda Kappa Medical Fraternity, Miami, Florida (March) 1960. 4. Clinical Reports to the Medical Dept., Armour Pharmaceutical Co., 1959.

in respiratory inflammation



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NOW... the first truly effective and safe control of both **chronic** and acute **diarrhea**

Sorboquel T.M.

(polycarbophil - thihexinol methylbromide)

IN CONVENIENT TABLET FORM

A totally new agent, for non-opiate control of the dual problem of diarrhea: too fluid feces, too frequent evacuations

Unexcelled therapeutic response, 85% of the chronic cases, 93% of the acute.[1-3]

The culmination of a decade of laboratory experimentation and over five years of clinical confirmation.

For too fluid feces, an extraordinary ability to absorb free fecal water.

For too frequent evacuations, superior, yet selective, antimotility action.

Convenient tablet form; simple, uncomplicated dosage schedule (1 tablet q.i.d.).

Even where all other agents have failed– Sorboquel arrests long-standing, uncontrolled, exhausting diarrheas

Unexcelled Therapeutic Response: Results of the Administration of Sorboquel Tablets[1-6]

	No. of Patients	*Response*		
		Excellent	*Good*	*Poor*
Chronic Diarrhea*	**485**	335	76	74
		84.7%		15.3%
Acute Diarrhea**	**332**	288	22	22
		93.4%		6.6%

*Chronic diarrheas include irritable bowel syndrome, regional enteritis, diverticulitis and ulcerative colitis, postantibiotic enteritis, malabsorption syndrome, radiation proctitis, surgically short-circuited intestinal states. Diarrhea had persisted for more than a year in a large percentage with bowel movement frequency averaging from 5 to more than 10 a day. In most patients, SORBOQUEL controlled the condition within 3 days, even where other agents had failed.

**Acute diarrheas include nonspecific gastroenteritis, enteritis, enterocolitis. Control of the diarrhea was achieved within 24 hours in most cases.

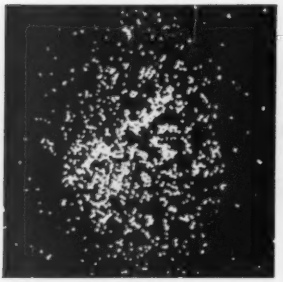
Dual-action **Sorboquel** arrests diarrhea even where all other agents have failed

The components in Sorboquel: the culmination of many years of development

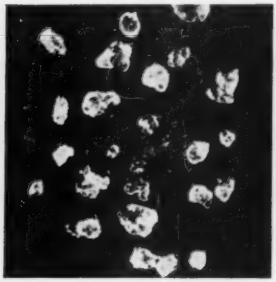
SORBOQUEL Tablets combine two unique and hitherto unavailable antidiarrheal agents—polycarbophil and thihexinol methylbromide. Acting together, through different but complementary mechanisms, these components in SORBOQUEL *absorb* free fecal water and *quell* hypermotility and associated spasm to an exceptional degree.

For too fluid feces, an extraordinary ability to absorb free fecal water

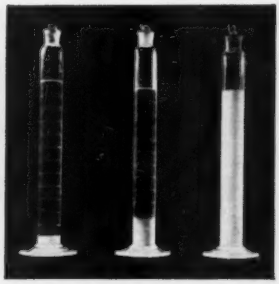
(through the hydrosorptive action of new polycarbophil)



Dry State
Demonstration of the particulate nature of dry polycarbophil.



Swollen State
Note the particulate nature of swollen polycarbophil. Impaction is virtually impossible.



(a) (b) (c)

Demonstration of the dependence of swelling of polycarbophil on pH (a) pH of stomach; (b) pH of duodenum; (c) pH of intestines.

A newly synthesized macromolecular substance exhibiting extraordinary capacity for absorption and retention of free fecal water[9-11] ■ the colloidal suspension is free-flowing, since, in the swollen or hydrated state, the particulate structure is retained[9] ■ exerts marked hydrosorptive action only on reaching the alkaline medium of the small intestine and colon ■ virtually free of impaction qualities ■ pharmacologically inert, not absorbed from the gut[12]

Convenient tablet form; simple, uncomplicated dosage schedule

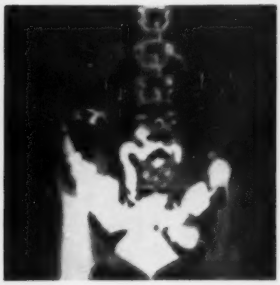
SORBOQUEL DOSAGE: For older children and adults, initial dosage of one SORBOQUEL Tablet q.i.d. is usually adequate. Severe diarrheas may require six, or even eight, tablets in divided daily doses. (Dosages exceeding six tablets a day should not be employed over prolonged periods.) Many patients can be maintained on one to three tablets daily after the diarrhea is brought under control.

SIDE EFFECTS: The incidence of side effects at recommended dosage is negligible. (The usual precautions when using parasympatholytic agents should be observed. ***Complete information regarding the use of*** SORBOQUEL TABLETS ***is available on request.***

DUAL ACTION Sorboquel TABLETS

the first truly effective agent to control the dual problem of diarrhea: too fluid feces, too frequent evacuations

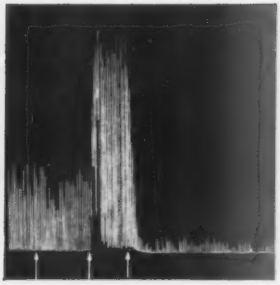
For too frequent evacuations, superior, yet selective, antimotility action
(through the parasympatholytic action of thihexinol methylbromide)



90-minute film demonstrating hypermotility of gastrointestinal tract in patient.



6-hour film after administration of thihexinol to patient showing marked inhibition of gastrointestinal motility.



(a) (b) (c)

Inhibition of methacholine-induced spasm by thihexinol in isolated rabbit intestine. Time of graph is 40 minutes. (a) normal motility; (b) methacholine, 40 mcg./L; (c) thihexinol, 10 mcg./ml.

A new, superior parasympatholytic agent with a dominant inhibitory action on intestinal motor function[13-16] ■ onset of intestinal motor inhibition has been shown to occur within *10-20 minutes*[14] ■ does not interfere with gastric secretion or digestive processes ■ unusually free from atropine-like side effects ■ its enteral antimotility action permits polycarbophil to exert maximal water-binding effect

SUPPLIED: SORBOQUEL TABLETS, bottles of 50 and 250. Each tablet contains 0.5 Gm. polycarbophil and 15 mg. thihexinol methylbromide.

REFERENCES: 1. Hock, C. W.: Med. Times **88**:320 (March) 1960. 2. Winkelstein, A.: Personal communication. 3. Berkowitz, D.: in press. 4. Lind, H. E.: Personal communication. 5. Seneca, H.: in press. 6. Riese, J. A.: Personal communication. 7. Gilbert, A. S., Schwartz, I. R., and Matzner, M. J.: Submitted for publication. 8. Personal communications to Medical Department, White Laboratories, Inc. 9. Pimparker, B. D.; Paustian, F. F.; Roth, J. L. A., and Bockus, H. L.: To be published. 10. Texter, E. C.: Personal communication. 11. Clinical reports to Medical Department, White Laboratories, Inc. 12. Grossman, A. J.; Batterman, R. C., and Leifer, P.: J. Am. Geriat. Soc. **5**:187 (Feb.) 1957. 13. McHardy, G.; Browne, D.; McHardy, R.; Bodet, C., and Ward, S.: Am. J. Gastroenterol. **24**:601 (Dec.) 1955. 14. Shay, H.: Personal communication. 15. Hirsh, H.: Personal communication. 16. Bercovitz, L. T.: J. Am. Geriat. Soc. **5**:940 (Nov.) 1957.

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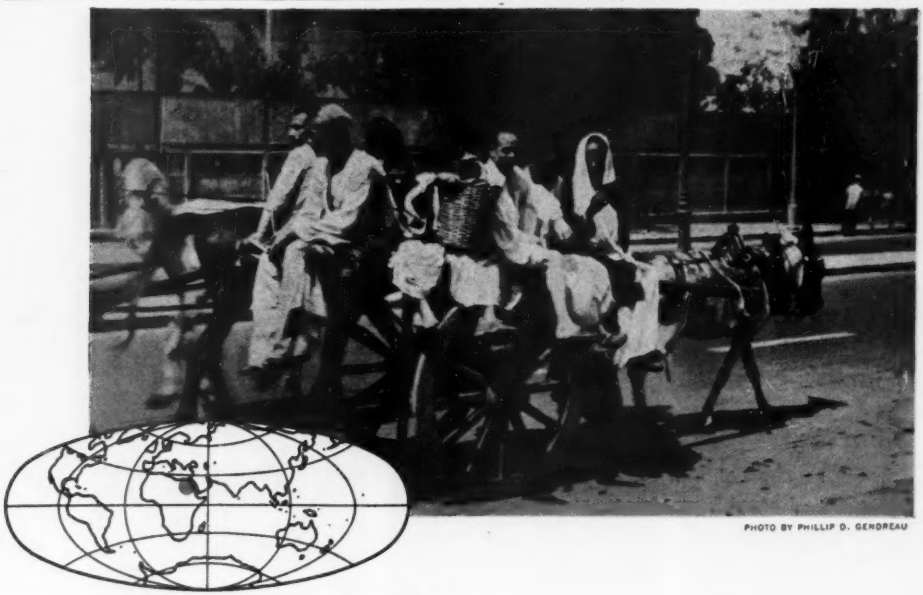


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world-wide evidence favors Furoxone for bacterial diarrheas

In Egypt, Furoxone® effective against shigella strains now resistant to other antimicrobials

Cairo investigators administered FUROXONE for one week to 37 patients with shigellosis, reported all 37 clinically cured, 35 free of shigella prior to completion of FUROXONE therapy.

FUROXONE was tested in light of evidence that shigella strains resistant to sulfonamides, tetracyclines and chloramphenicol now exist. Observations: "All shigella isolated were sensitive in vitro to [FUROXONE]". Clinically, FUROXONE "significantly reduces the duration and severity of the diarrhea and effects bacteriological cure .... The absence of toxic or side effects gives [FUROXONE] an advantage not possessed by the other drugs in current use."

Musgrave, M. E. and Arm, H. G.: Antibiotic Med. & Clin. Therapy 7:17 (Jan.) 1960.

FUROXONE LIQUID: a pleasant orange-mint flavored suspension containing FUROXONE 50 mg. per 15 cc., with kaolin and pectin ■ for patients of all ages (may be mixed with infant formulas, passes through a standard nursing nipple) ■ Supply: bottles of 240 cc. **FUROXONE TABLETS:** 100 mg., scored, bottles of 20 and 100.

DOSAGE: should provide (in 4 divided doses) 400 mg. daily for adults, 5 mg./Kg. daily for children.

FUROXONE

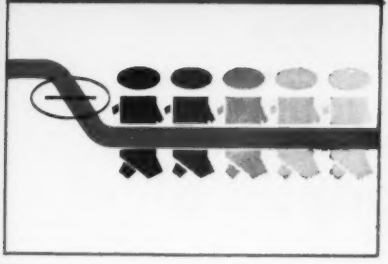
THE NITROFURANS —a *unique* class of antimicrobials

EATON LABORATORIES, NORWICH, NEW YORK

making oral blood-sugar control a reality for more diabetics

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brand of chlorpropamide



IN BRIEF

DIABINESE, a potent sulfonylurea, provides smooth, long-lasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, DIABINESE often works where other agents have failed to give satisfactory control.

INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: Many side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea, (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

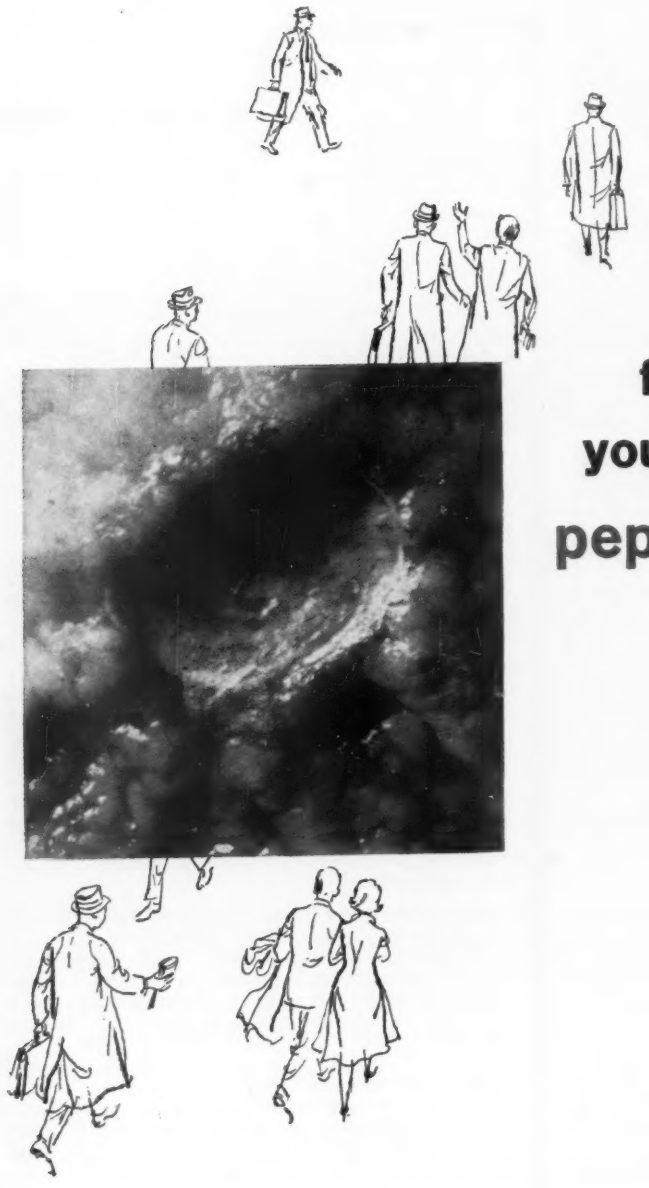
SUPPLIED: As 100 mg. and 250 mg. scored chlorpropamide tablets.

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for
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peptic ulcer
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TABLETS SUSPENSION

ALUDROX®

Aluminum Hydroxide Gel with Magnesium Hydroxide, Wyeth

SIMPLE ACIDITY CONTROL

The crux of drug therapy in peptic ulcer is control of gastric acidity. ALUDROX provides physiologic neutralization in the range of pH 3 to 5—pepsin is inactivated.

The 4:1 combination of aluminum hydroxide and magnesium hydroxide in ALUDROX is time-proved. ALUDROX relieves pain, promotes healing with no fear of gastrin stimulation or induced constipation. With ALUDROX, there is no complication of existing constipation.

Added to the other elements in the regimen you have selected, ALUDROX can facilitate management of peptic ulcer.

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. basic or comprehensive drug therapy

ALUDROX® SA

Suspension and Tablets: Aluminum Hydroxide Gel with Magnesium Hydroxide, Ambutonium Bromide and Butabarbital, Wyeth

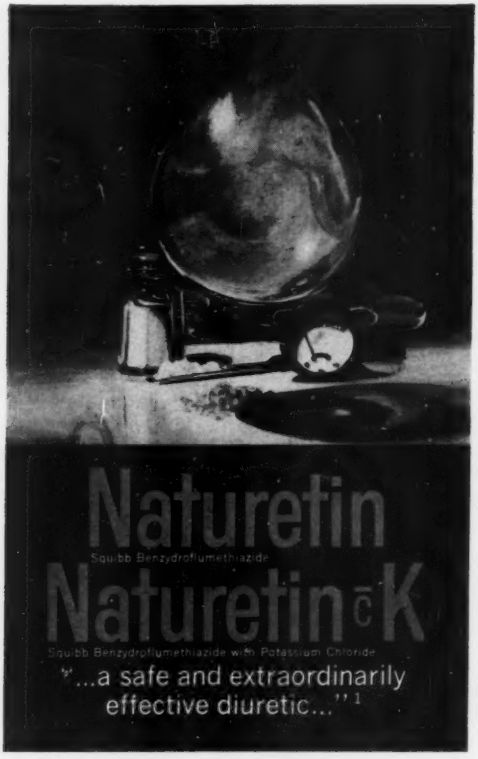
FUNDAMENTAL ACIDITY CONTROL...PLUS

When your patient requires more than simple acidity control, ALUDROX SA is a drug of choice. ALUDROX SA provides control of acidity and calms emotional distress, promotes healing, inhibits gastric mobility, and relieves pain. It provides these benefits because it is antacid, pepsin-inhibiting, anticholinergic, demulcent, and anticonstipant.

The use of this single comprehensive formula rather than separate agents is more convenient for both patient and physician.

For further information on prescribing and administering ALUDROX SA and ALUDROX see descriptive literature, available on request.

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Naturetin — reliable therapy in edema and hypertension — maintains a favorable urinary sodium-potassium excretion ratio . . . retains a balanced electrolytic pattern:

"...the increase in urinary output occurs promptly..."[1]

"...the least likely to invoke a negative potassium balance..."[2]

"...a dose of 5 mg. of Naturetin produces a maximal sodium loss."[2]

"...an effective diuretic agent as manifested by the loss in weight..."[3]

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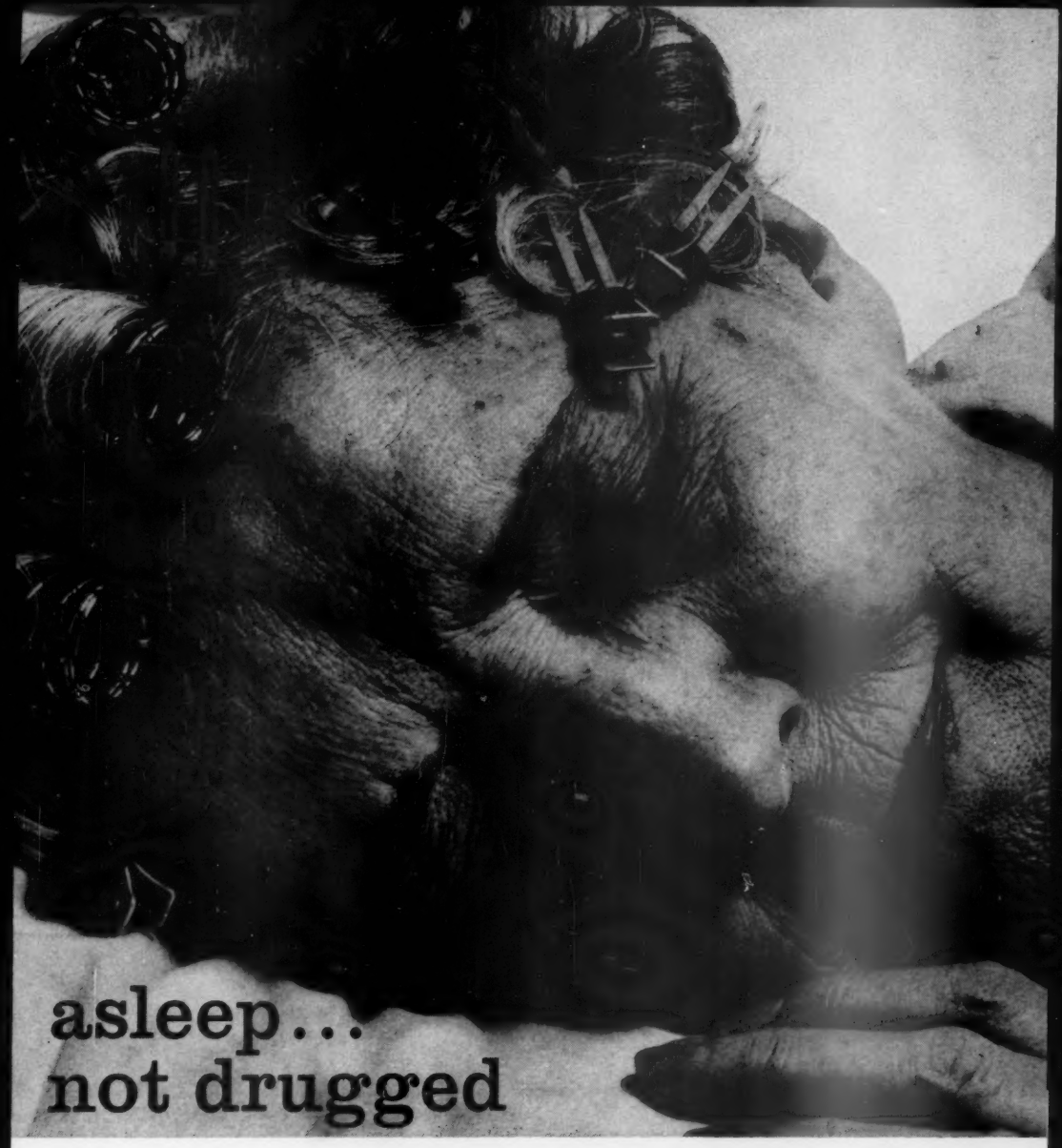
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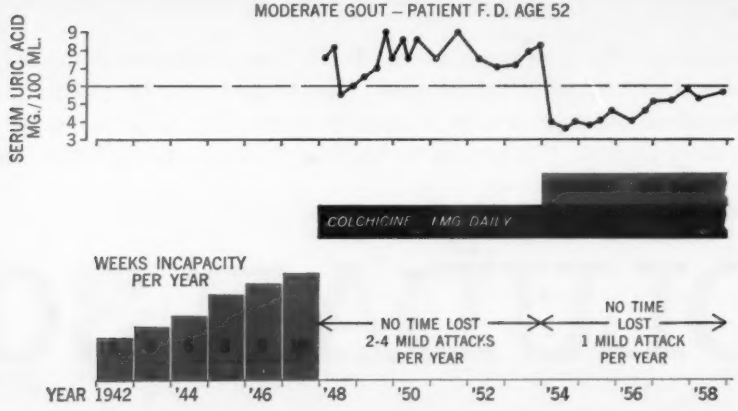
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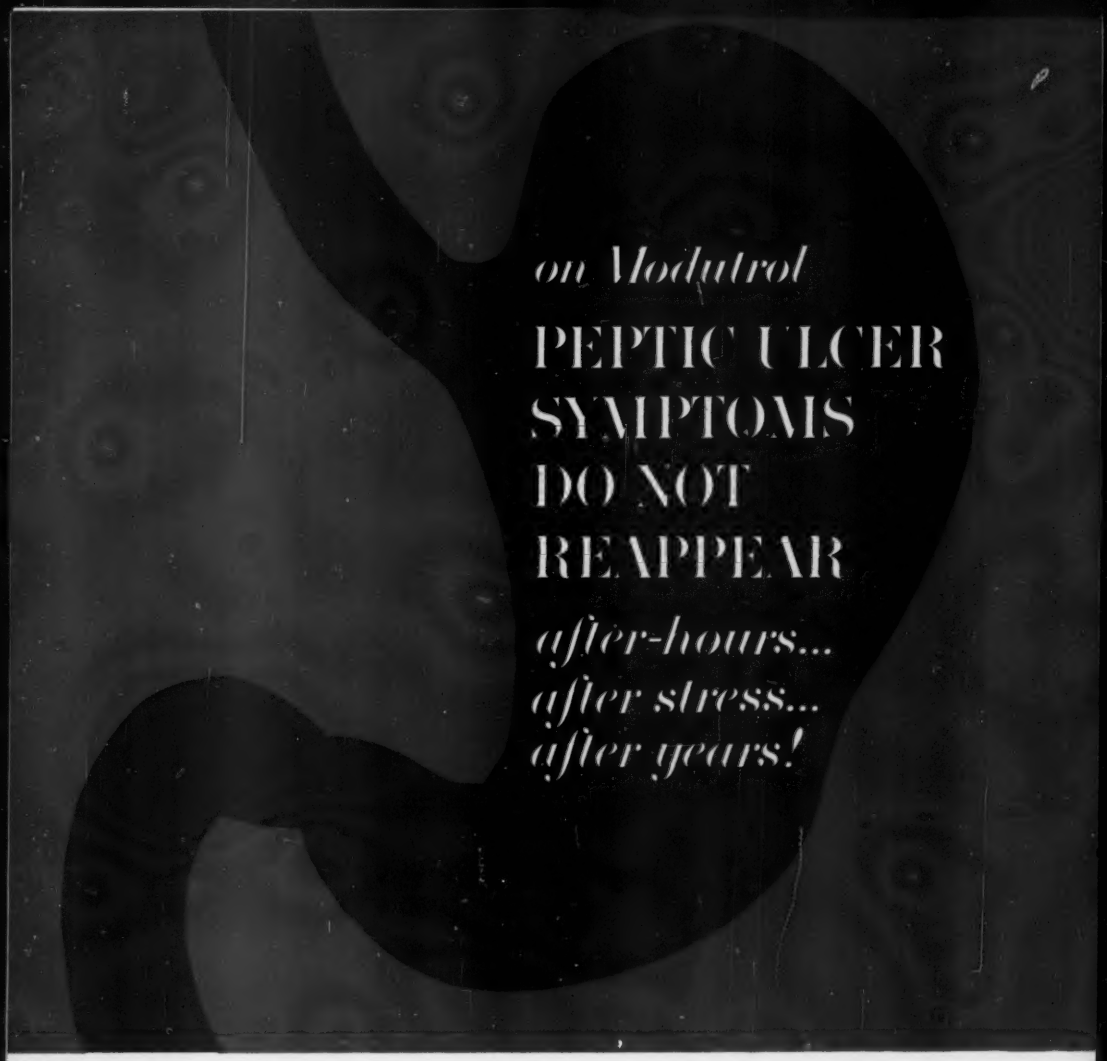
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1. Rosenblum, L. A.: Report, Symposium on Peptic Ulcer, University of Vermont School of Medicine, September 24, 1959.

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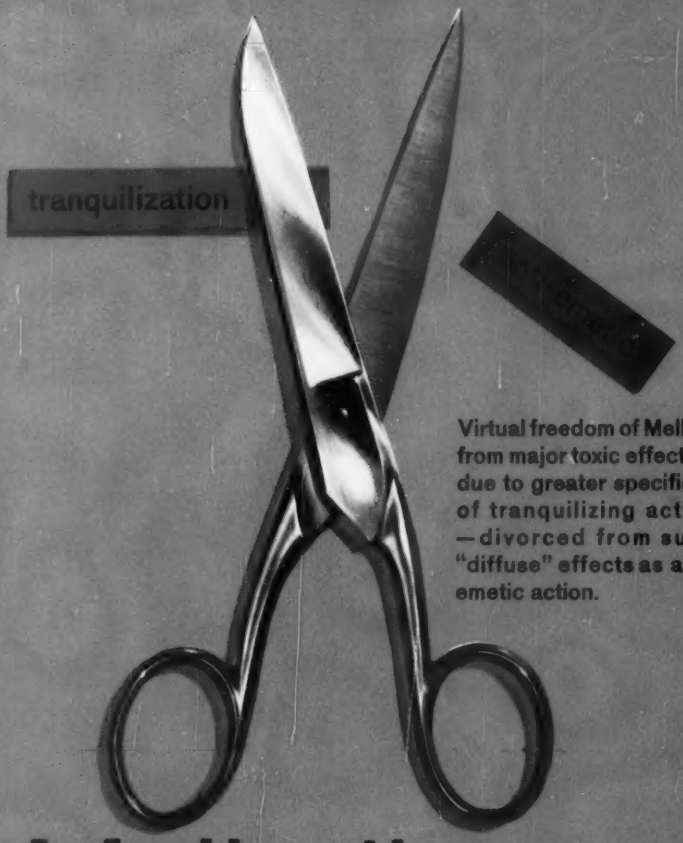
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*Kinross-Wright, J.: Newer phenothiazine drugs in treatment of nervous disorders, J.A.M.A. 170:1283, July 11, 1959.

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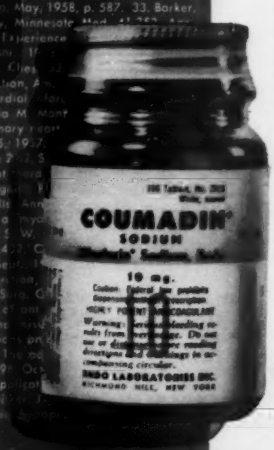
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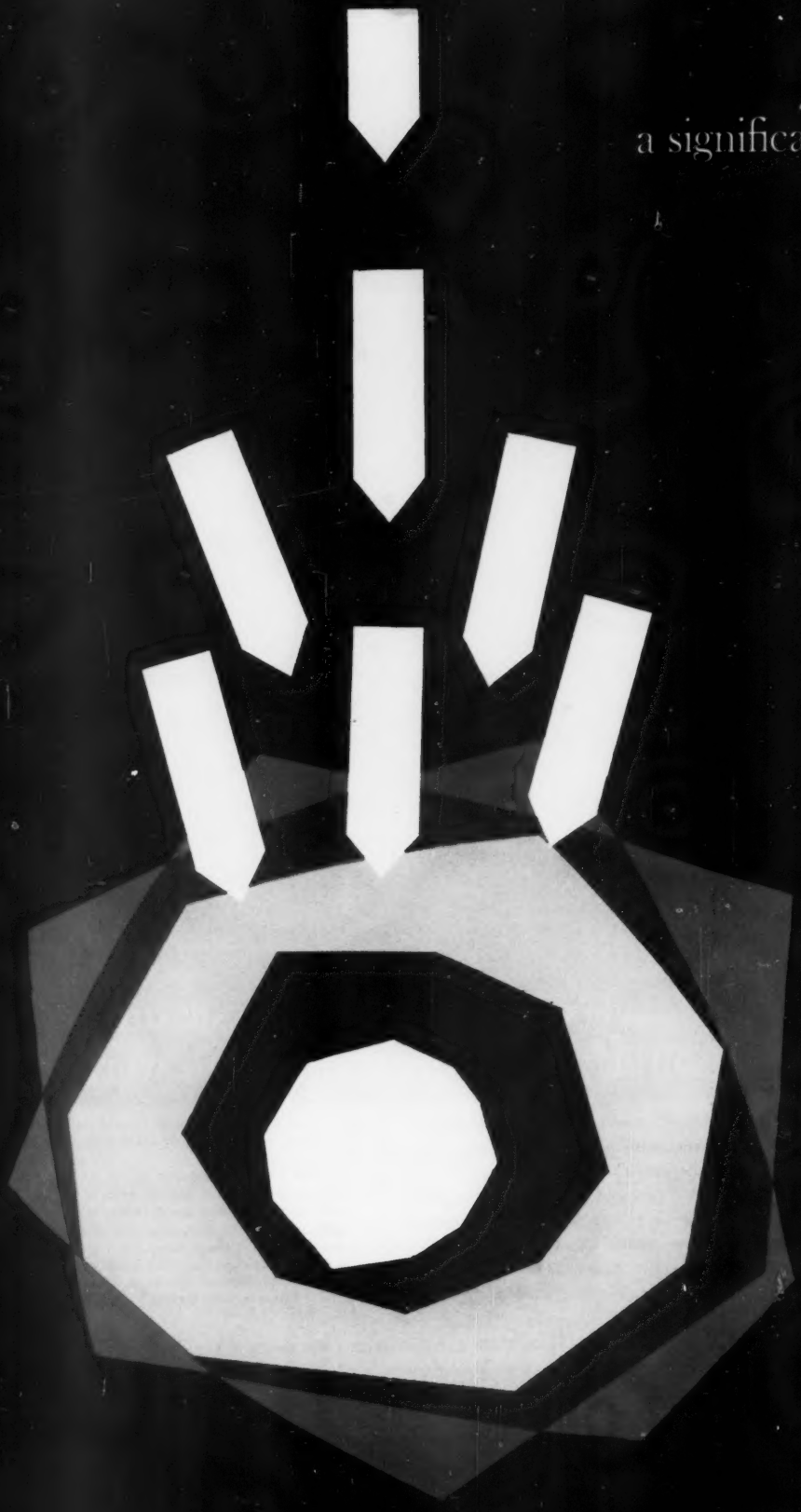
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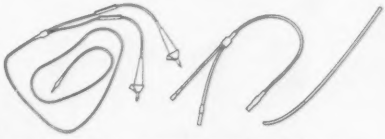
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in the special diet patient improve nutrition . . . promote better health with

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Therapeutic B Factors with Vitamin C

A single capsule provides 250 mg. of vitamin C and massive doses of B factors to meet the need when requirements are high and reserves are low. Prescribe "Beminal" Forte for patients on special diets, pre- and postoperatively, and during convalescence, to improve the prognosis and accelerate recovery.

Supplied: No. 817 — Bottles of 100 and 1,000 capsules.

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chemical name:
1-m-aminophenyl-2-pyridone
generic name:
amphenidone

with selective action on the central nervous system at both the cerebral and cord levels.

for the treatment of anxiety & tension without causing drowsiness

Dornwal is regarded as a tranquilizer best suited for ambulatory patients.

- does not produce depression or depersonalization
- relieves acute emotional upsets
- relieves tension without undue stimulation
- effectively interrupts tension headaches
- is virtually devoid of sedative activity

Dornwal has proved to be relatively free from side effects when administered at recommended dosage. In 593 patients the incidence of drowsiness was less than 2 per cent — statistically not significant.

Prescribe Dornwal for your next patient who needs a tranquilizer but cannot afford to be drowsy. Write for your trial supply.

Indications: anxiety and tension, various types of psychoneuroses, menopausal syndrome, tension headache, alcoholism, premenstrual tension, behavior problems in children.

Dosage: One or two 200 mg. tablets three times a day. Children, one or two 100 mg. tablets two times a day. Administration limited to three months duration.

Supplied: 200 mg. yellow scored tablets, and 100 mg. pink tablets, each in bottles of 100 and 500.

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PDL-03

RONCOVITE®-MF IS RAPIDLY BECOMING THE DRUG OF CHOICE IN ANTI-ANEMIA THERAPY...

because...

Cobalt is the only clinically proved therapeutic agent which enhances the formation of erythropoietin, the hormone which regulates erythropoiesis in the body.[1-3]

because...

Roncovite through the effect of Cobalt-enhanced erythropoietin improves iron utilization by activating this normal physiologic process.[3-4]

because...

The result is a more rapid and complete hematologic response in the anemic patient . . .[5-9]

and because...

The safety of Roncovite has been thoroughly attested in published literature and demonstrated during the administration of over 365 million doses.[6,10,11]

1. Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. F.: Blood *13*:55 (Jan.) 1958. 2. Murdock, H. R. Jr.: Am. Pharm. Assoc. (Sci. Ed.) *48*:140, 1959. 3. Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L.: Science *125*:1085 (May 31) 1957. 4. Center, W. M.: Clin. Med. *7*:713 (April) 1960. 5. Holly, R. G.: Obst. & Gynec. *9*:299 (Mar.) 1957. 6. Ausman, D. C.: Journal-Lancet *76*:290 (Oct.) 1956. 7. Flynn, R. T.: Therapy with Cobalt and Iron for Correction of Anemia in Pregnancy, Presented at Michigan and Wayne Co. Acad. GP, Postgrad. Clinic, Detroit, Mich., Nov. 11-12, 1959. 8. Tevetoglu, F., and Ozkaragoz, K.: M. Times *86*:81 (Jan.) 1958. 9. Craig, P. E.: Clin. Med. *6*:597 (April) 1959. 10. Hill, J. M.; LaJous, J., and Sebastian, F. J.: Cobalt Therapy in Anemia, Texas J. Med. *51*:686 (Oct.) 1955. 11. Tevetoglu, F.: J. Pediat. *49*:46 (July) 1956.

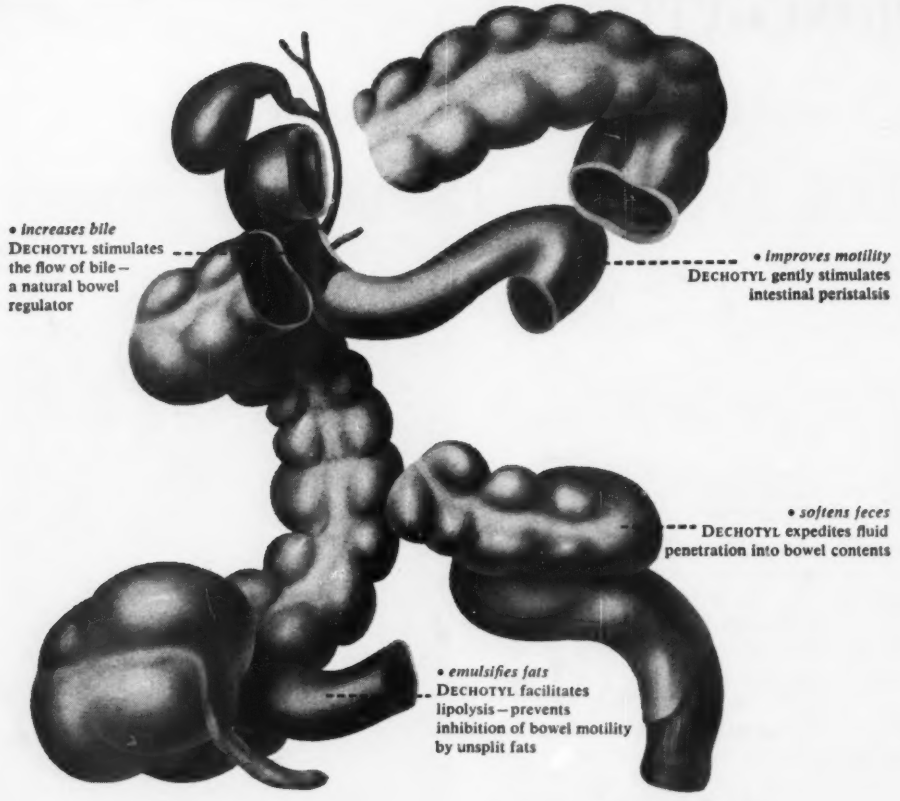
Please write for monograph, "The Hormone Erythropoietin." Roncovite literature also available on request.

EACH ENTERIC COATED, GREEN TABLET CONTAINS:

Cobalt chloride . . . . . 15 mg.
(Cobalt as Co. 3.7 mg.)
Ferrous sulfate, exsiccated . . . . . 100 mg.

DOSAGE: The maximum adult dose of Roncovite-MF is one tablet after each meal and at bedtime.

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helps free your patient from both...
constipation and laxatives

DECHOTYL®

TRABLETS*

well tolerated...gentle transition to normal bowel function

Recommended to help convert the patient—naturally and gradually—to healthy bowel habits. Regimens of one week or more are suggested to assure maintenance of normal rhythm and to avoid the repetition of either laxative abuse or constipation.

Average adult dose: Two TRABLETS at bedtime as needed or as directed by a physician. *Action usually is gradual, and some patients may need 1 or 2* TRABLETS *3 or 4 times daily.*

Contraindications: Biliary tract obstruction; acute hepatitis.

DECHOTYL TRABLETS provide 200 mg. DECHOLIN,® (dehydrocholic acid, AMES), 50 mg. desoxycholic acid, and 50 mg. dioctyl sodium sulfosuccinate, in each trapezoid-shaped, yellow TRABLET. Bottles of 100.

*AMES T.M. for trapezoid-shaped tablet.

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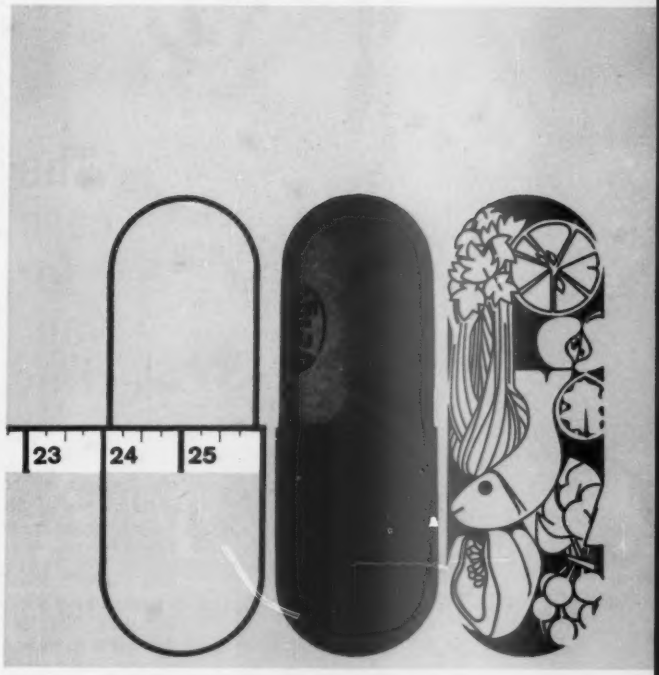
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brand of phenmetrazine HCl with vitamins and minerals

Now, Prelu-Vite helps to fortify the patient's nutritional status and sense of well-being without jeopardizing the success of the weight-reducing program.

By improving nutritional status Prelu-Vite makes it easier for the patient to retain the initial zeal for reducing...facilitates the retention of enthusiastic cooperation in pursuing therapy to a successful conclusion.

With Prelu-Vite, as with Preludin, a weight loss 2–5 times that obtainable by dietary restriction alone, is readily achieved without the occurrence of annoying side reactions.



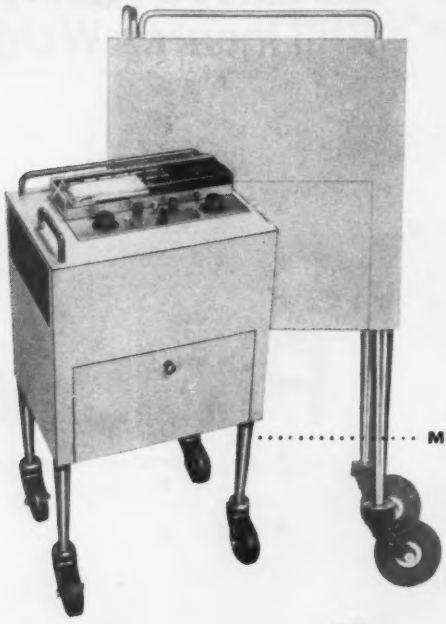
Geigy

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Under license from C. H. Boehringer Sohn, Ingelheim.

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Geigy, Ardsley, New York

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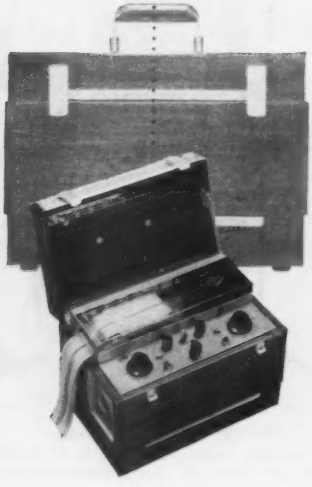


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The case for your electrocardiograph

Why not just one "all-purpose" electrocardiograph — for house calls . . . office use with a choice of chart speeds, sensitivities, recording capabilities . . . mobile "heart station" use in clinics and hospitals? Because *each* need calls for *specific, individual* instrument characteristics — as found in these three Sanborn electrocardiographs.

The Sanborn Model 300 Visette weighs only 18 pounds, is as small as a brief case, has rugged, largely transistorized circuitry. *The Model 100 Viso-Cardiette* is also portable, but expressly designed for use where the versatility of *two* chart speeds, *three* sensitivities, and provision for *monitoring* and *other* types of recording are desired. The third Sanborn instrument is the *Model 100M "Mobile Viso"* — identical in circuitry to the 100, but in a mobile cabinet of either mahogany or rugged, stain-resistant plastic laminate.

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in urologic patients taking MANDELAMINE®

brand of methenamine mandelate

This is why Mandelamine is a most effective urinary antibacterial, especially for stubborn disorders. Urine-specific Mandelamine eradicates most pathogens commonly encountered in chronic urinary infections—even strains resistant to antibiotics and sulfonamides. Mandelamine—antibacterial, but *not* an antibiotic—does not produce resistant mutants. And systemic reactions are rarely seen. Mandelamine... effective, well-tolerated, economical. Average adult dose, 2 Mandelamine Hafgrams® q.i.d.

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in pain, such as that of cancer, Thorazine®,

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one of the fundamental drugs in medicine, reduces by potentiation the amount of narcotic needed; alleviates the anxiety that intensifies suffering; improves the patient's mental outlook. Also, controls nausea and vomiting.



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STOPS IN 30 MINUTES!

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PYRIDIUM®

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Patients on Pyridium experience welcome relief from urinary pain, burning, frequency and urgency—usually within 30 minutes. And Pyridium may be given with *any* urinary antibacterial. In fact, its recommended daily dosage of two 0.1-Gm. tablets t.i.d. provides a greater analgesic effect in adults than the recommended daily dosage of many fixed antibacterial-analgesic combinations. Because Pyridium is extremely well tolerated, you can provide pain relief until the underlying infection is completely controlled with the antibacterial of your choice. So next time you see a patient with a painful urinary infection, prescribe Pyridium.

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QUIESCENCE

for the medical patient in situational stress

PHENERGAN—available in four convenient forms—helps you cope with situational stress so frequently met in the practice of medicine. Whatever dosage form you choose, PHENERGAN provides these benefits:

quiescence—relief of apprehension; nighttime, perisurgical, obstetrical

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INJECTION • TABLETS • SYRUP • SUPPOSITORIES

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Bathsheba at her toilet
by Rembrandt.

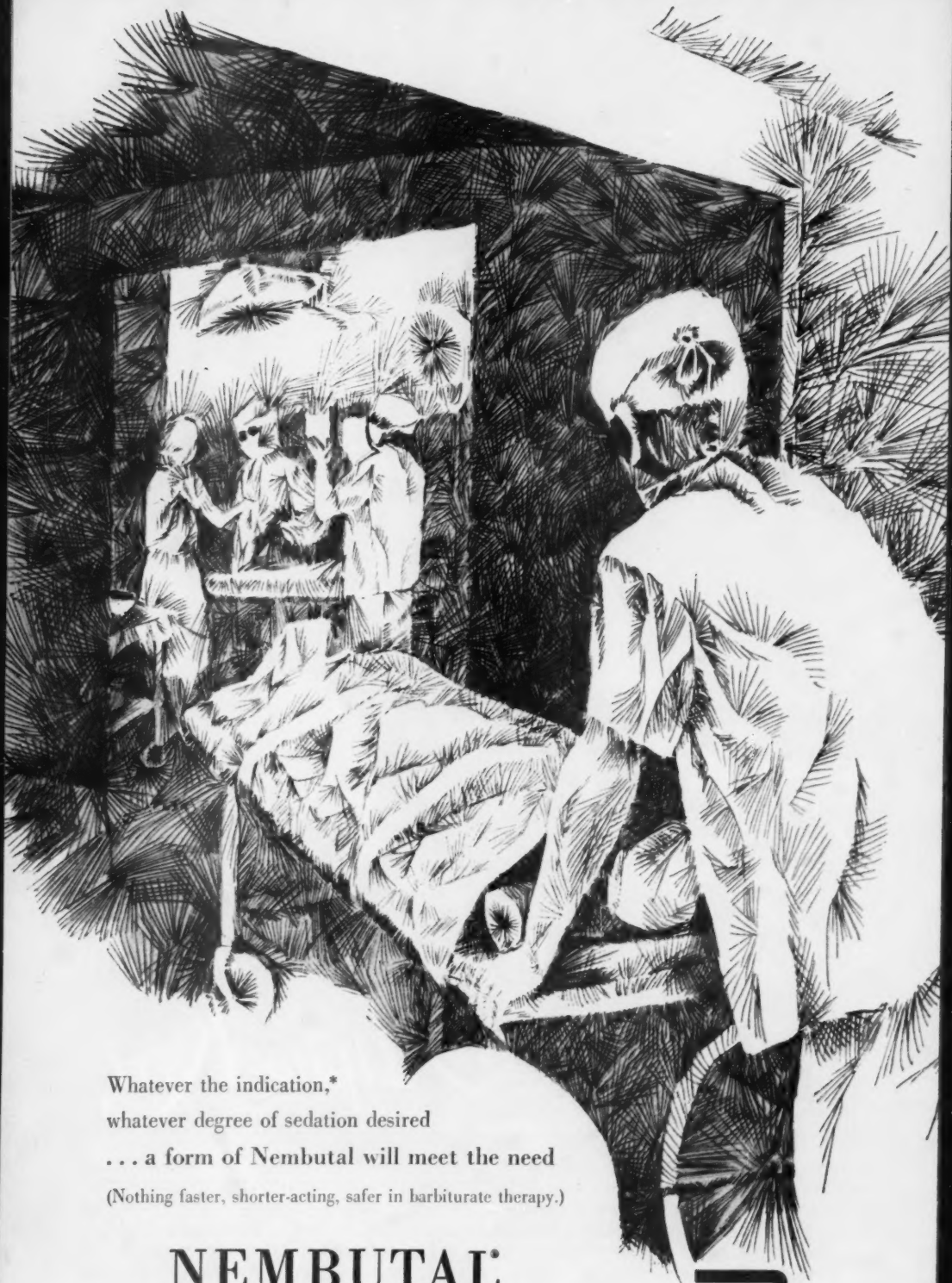
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Alpha-KERI makes dry skin feel soft and smooth immediately. It effectively deposits a uniform, partially occlusive oil film over the entire skin area. Alpha-KERI lubricates the skin, relieves itching and restores the protective action of natural skin oils lost by the action of water, weather and detergents. It moisturizes the skin and also helps to retain moisture by retarding evaporation of water. Alpha-KERI contains: Kerohydric®, brand of dewaxed, oil-soluble, keratin-moisturizing fraction of lanolin, mineral oil, and a special nonionic emulsifier which provides the right amount of water dispersibility for optimum coverage of the skin with emollient oils. Alpha-KERI oil may be used in the bath, in the shower, for sponge bathing and for infant baths. It can also be used for skin cleansing where soap is contraindicated. Alpha-KERI oil is tinted an attractive green color and pleasantly scented. Bottles of 8 fl. oz. *Write for samples and literature.*

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Whatever the indication,*
whatever degree of sedation desired
. . . a form of Nembutal will meet the need
(Nothing faster, shorter-acting, safer in barbiturate therapy.)

NEMBUTAL®

(Pentobarbital, Abbott)

*PREOPERATIVE SEDATION

ABBOTT

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Squibb Announces Chemipen

Squibb Alpha-Phenoxyethyl Penicillin Potassium

new chemically improved penicillin which provides the highest blood levels that are obtainable with oral penicillin therapy



As a pioneer and leader in penicillin therapy for more than a decade, Squibb is pleased to make Chemipen, a new chemically improved oral penicillin, available for clinical use.

With Chemipen it becomes possible as well as convenient for the physician to achieve and maintain higher blood levels—with greater speed—than those produced with comparable therapeutic doses of potassium penicillin V. In fact, Chemipen is shown to have a 2:1 superiority in producing peak blood levels over potassium penicillin V.*

Extreme solubility may contribute to the higher blood levels that are so notable with Chemipen.* Equally notable is the remarkable resistance to acid decomposition (Chemipen is stable at 37°C. at pH 2 to pH 3), which in turn makes possible the convenience of oral treatment.

And the economy for your patients will be of particular interest—Chemipen costs no more than comparable penicillin V preparations.

Dosage: Doses of 125 mg. (200,000 u.) or 250 mg. (400,000 u.), t.i.d., depending on the severity of the infection. The usual precautions must be carefully observed with Chemipen, as with all penicillins. Detailed information is available on request from the Professional Service Department.

Supply: Chemipen Tablets of 125 mg. (200,000 u.) and 250 mg. (400,000 u.), bottles of 24 tablets. Chemipen Syrup (cherry-mint flavored, nonalcoholic), 125 mg. per 5 cc., 60 cc. bottles.

*Knudsen, E. T., and Rolinson, G. N.: Lancet 2:1105 (Dec. 19) 1959.

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Squibb Quality—the Priceless Ingredient

in premenstrual tension



clinicians report rapid relief with

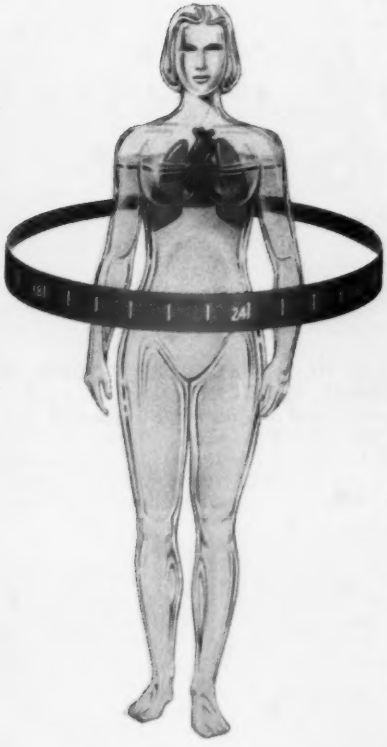
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increased potency–without corresponding increase in side effects

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Fuchs, M. and Moyer, J.:
Diseases of the Chest 35:314, (March) 1959.



"Premenstrual edema is present in 40% of women and...consists of weight gain, subcutaneous edema, emotional lability, breast turgidity, anxiety and tension." In addition to controlling the objective symptoms of premenstrual tension, HYDRODIURIL may afford relief of subjective complaints including tension, nervousness and headache.

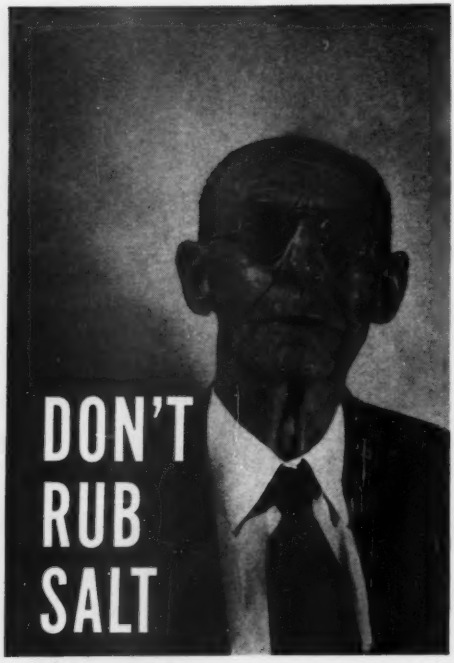
DOSAGE: 25 to 50 mg. of HYDRODIURIL once or twice a day, beginning the first morning of symptoms and continuing until the onset of the menses.

SUPPLIED: 25 and 50 mg. scored tablets HYDRODIURIL (hydrochlorothiazide) in bottles of 100 and 1,000.

HYDRODIURIL is a trademark of Merck & Co., INC.

Additional information on HYDRODIURIL is available to the physician on request.

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IN HIS CARDIAC WOUND

Modern saluretics may *seem* to have made unlimited salt intake possible for cardiac and hypertensive patients. Yet despite the improvements in diuretic therapy, sodium restriction is still important in the prophylaxis of edema. The wise physician does not add needlessly to the burden of his patient, nor test unnecessarily the power of the drugs he prescribes. It makes good sense to him to prescribe DIASAL—which looks, tastes and flavors food exactly like salt . . . but is sodium free.

Diasal contains potassium chloride, glutamic acid and inert ingredients. Supplied in shakers and 8 oz. bottles.

prescribe DIASAL®
sodium-free salt substitute

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THE AMERICAN COLLEGE OF PHYSICIANS

Postgraduate Courses, Autumn-Winter, 1960-61

COURSE NO. 1, HEMATOLOGY AND RADIOISOTOPES: The Ohio State University College of Medicine, Columbus, Ohio; Charles A. Doan, M.D., F.A.C.P., Director; September 19–23, 1960.

COURSE NO. 2, CANCER AND THE INTERNIST—1960 CONCEPTS: Memorial Center, Sloan-Kettering Institute for Cancer Research, New York, N. Y.; Rulon W. Rawson, M.D., F.A.C.P., Director; October 10–14, 1960.

COURSE NO. 3, ELECTROCARDIOGRAPHY: University of Utah College of Medicine, Salt Lake City, Utah; Hans H. Hecht, M.D., F.A.C.P., Director; November 7–11, 1960.

COURSE NO. 4, RECENT ADVANCES IN DRUG THERAPY: University of Washington School of Medicine, Seattle, Wash.; Robert H. Williams, M.D., F.A.C.P., Director; January 9–13, 1961.

COURSE NO. 5, MECHANISMS OF DISEASE: Columbia University College of Physicians and Surgeons, Presbyterian Hosp., New York, N. Y.; Alfred P. Fishman, M.D., F.A.C.P., and Stanley E. Bradley, M.D., F.A.C.P., Co-Directors; January 16–20, 1961.

COURSE NO. 6, SELECTED TOPICS IN INTERNAL MEDICINE: The University of Oklahoma School of Medicine and University Hospitals, Oklahoma City, Okla.; Stewart G. Wolf, Jr., M.D., F.A.C.P., and James F. Hammarsten, M.D., F.A.C.P., Co-Directors; William O. Smith, M.D. (Associate) Associate Director; February 20–24, 1961.

The following courses are scheduled for Spring, 1961: CARDIOVASCULAR DISEASES, Mt. Sinai Hosp., March 6–10; ENDOCRINOLOGY, Univ. of Va., March 23–25; PROBLEMS OF GROWTH AND AGING, Lankenau Med. Bldg., Philadelphia, April 12–15; GASTROENTEROLOGY, Univ. of Penna., in May. Dates not set for following: ADVANCES IN ELECTROCARDIOGRAPHY, Univ. of Tenn.; INTERNAL MEDICINE, McGill Univ.

All courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. Tuition fee: Members, $60.00; Non-members, $80.00. Registration forms and requests for information to be directed to: Edward C. Rosenow, Jr., M.D., Executive Director, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

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quietly calming
You can prescribe gentle control of blood pressure with
BUTISERPINE®
Butiserpine contains *just enough* reserpine (0.1 mg. per tablet or teaspoonful) to reduce tension without initiating side effects; 15 mg. of BUTISOL sodium® butabarbital sodium, to promote calmness without lethargy.
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Your surgical convalescent feels better because he is better with

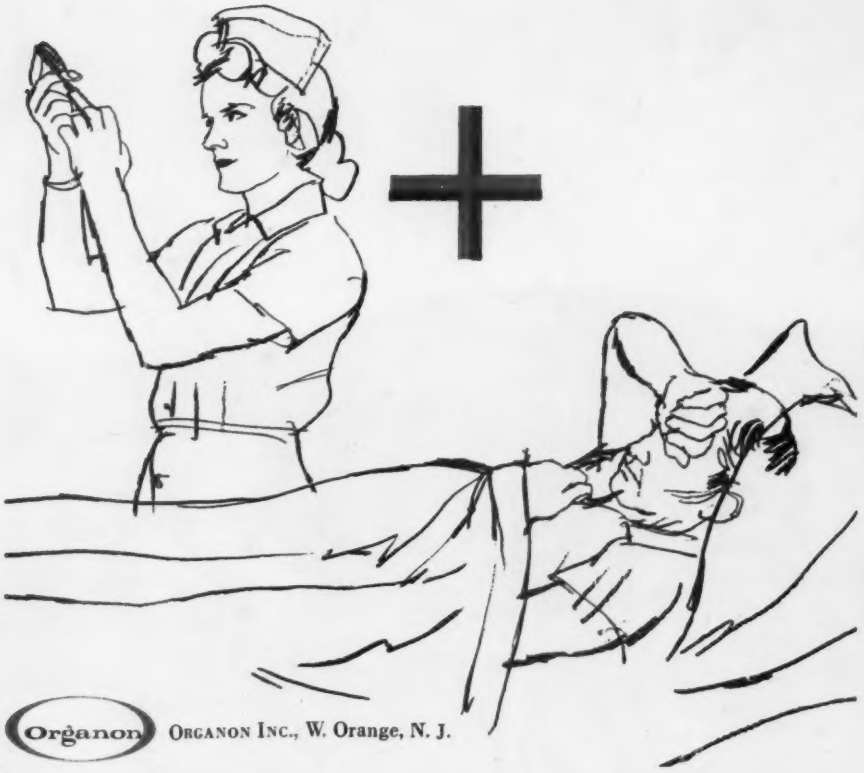
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1 cc. once each week

for safe potent anabolic stimulation
+ to maintain positive nitrogen balance
+ to promote rapid wound healing
+ to restore appetite, strength, vitality
+ to shorten convalescence, save nursing time
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Supplied: 1-cc. ampuls (box of three) and 5-cc. vials, 25 mg. nandrolone phenpropionate/cc.
Adults: 1 cc. i.m. each week, or 2 cc. every other week.



Organon ORGANON INC., W. Orange, N. J.



The physician listens to a tense, nervous patient discuss her emotional problems. To help her, he prescribes Meprospan (400 mg.), the only continuous-release form of meprobamate.



The patient takes one Meprospan-400 capsule at breakfast. She has been suffering from recurring states of anxiety which have no organic etiology.



She stays calm while on Meprospan, even under the pressure of busy, crowded supermarket shopping. And she is not likely to experience any autonomic side reactions, sleepiness or other discomfort.



She takes another capsule of Meprospan-400 with her evening meal. She has enjoyed sustained tranquilization all day—and has had no between-dose letdowns. Now she can enjoy sustained tranquilization all through the night.



Relaxed, alert, attentive . . . she is able to listen carefully to P.T.A. proposals. For Meprospan does not affect either her mental or her physical efficiency.



Peacefully asleep . . . she rests, undisturbed by nervousness or tension. (Literature on Meprospan is available from Wallace Laboratories, Cranbury, N. J.)

CME-2084

Each tablet contains:
Provera (medroxyprogesterone acetate) 2.5 mg.
Cardrase (ethoxzolamide) ..... 35 mg.
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DOSAGE: 1 tablet 1 or 2 times daily, 5-10 days before the period.

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GETS AT THE CAUSE

to restore hormonal balance...

corrective therapy Because Cytran contains the new progestin, Provera,† you can now reach the *cause* of premenstrual tension—hormonal imbalance. Estrogen-progesterone ratio is adjusted to more normal premenstrual balance. Thus even abdominal discomfort, shakiness, fatigue—symptoms incompletely controlled by mere symptomatic treatments—are effectively relieved.



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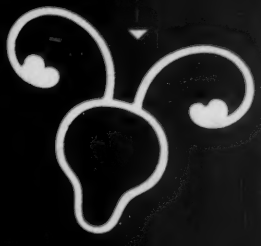
symptomatic therapy An effective diuretic (Cardrase†) and a mild tranquilizer (Levanil†) afford symptomatic relief while Provera works to effect a restoration of hormonal balance. They also supplement the activity of Provera in those rare cases where restoration of hormone balance does not completely eliminate edema and anxiety/tension.

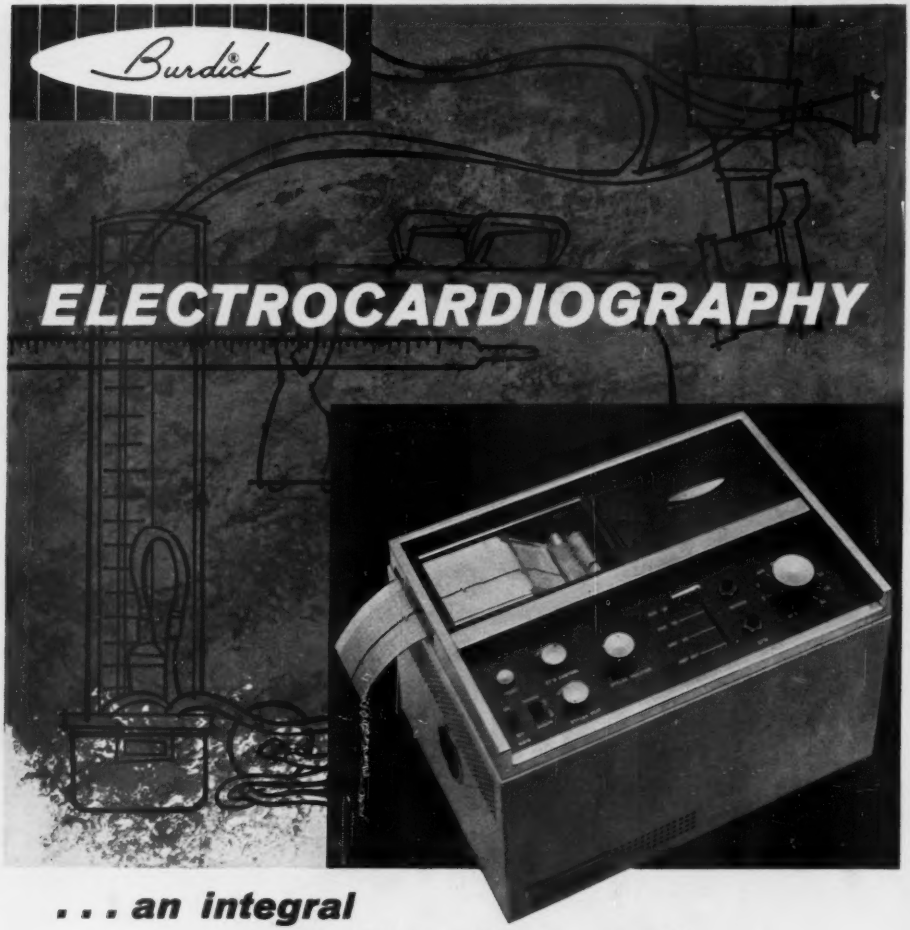
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Has the diagnostic equipment in your office kept pace with your own knowledge of new drugs, medicines and therapeutic technics? If not—call in your Burdick man!

He'll bring you up to date on the latest advances in electromedical instrumentation—as for example, the Burdick dual-speed electrocardiograph. Determine your net cost of new equipment, taking into consideration the income tax savings from annual depreciation allowances. This can make the purchase of new professional equipment far more attractive financially than you may have realized!

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emotional stress **and** overweight **often go hand in hand...**



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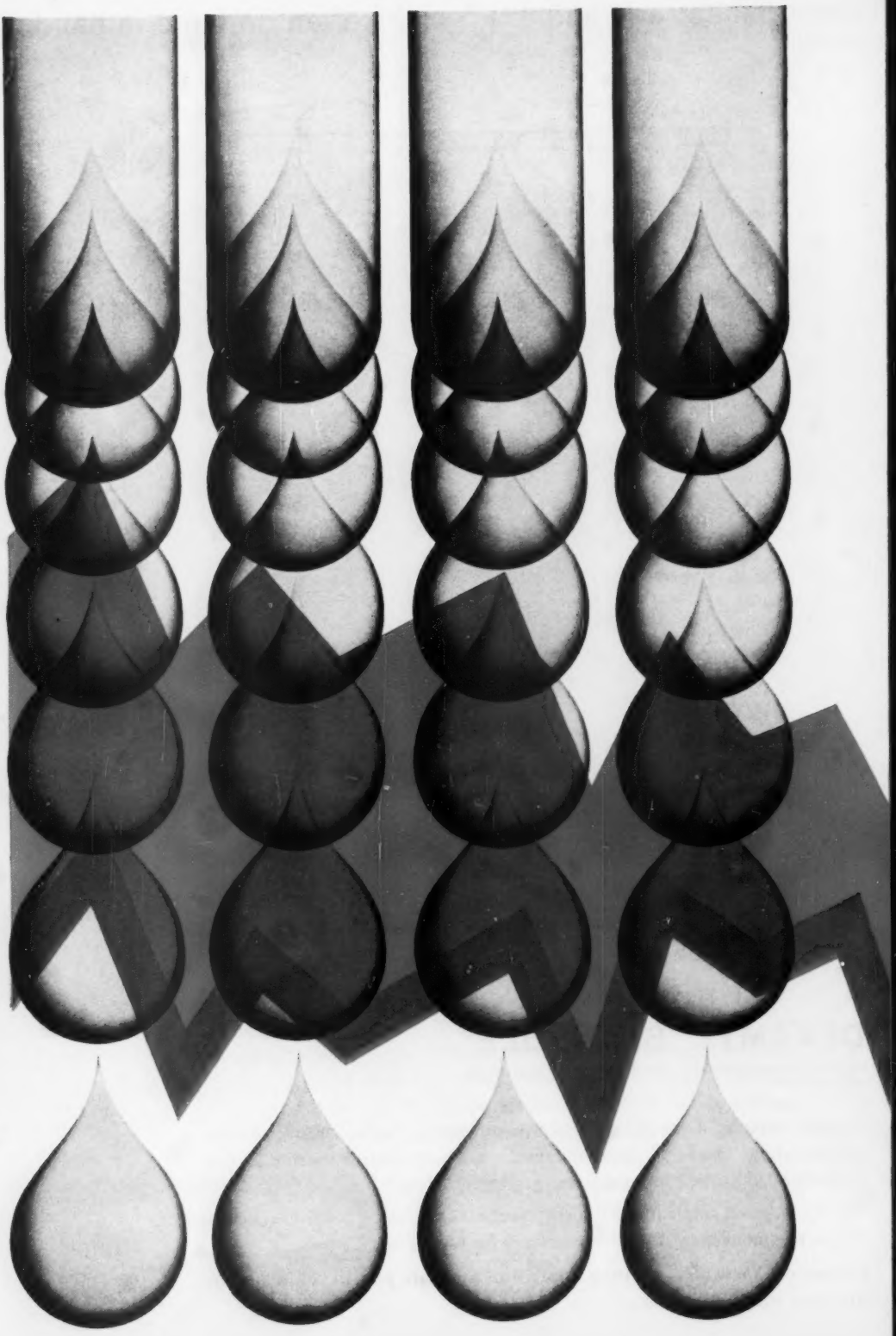
brand of dextro amphetamine and amobarbital

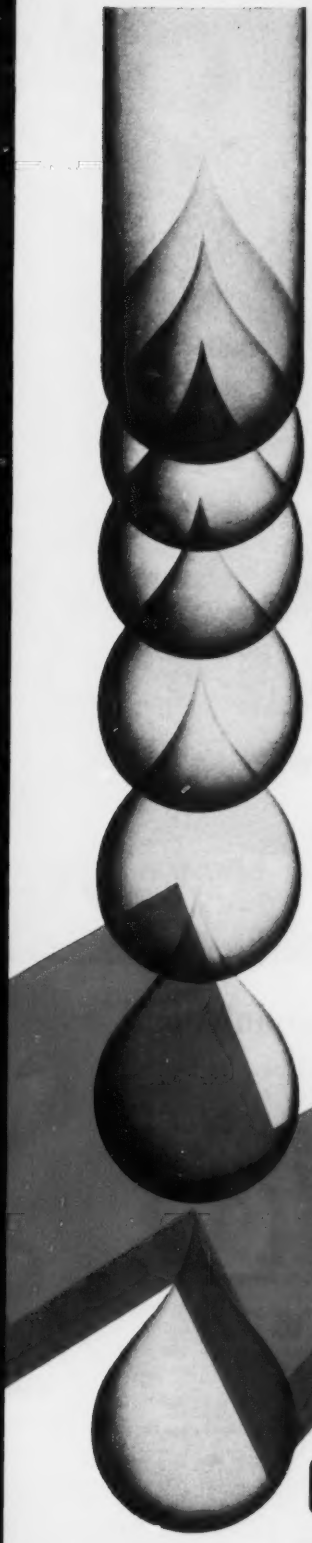
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In tense, nervous, depressed patients who attempt to "solve" their problems by overeating, 'Dexamyl' *Spansule* capsules not only control appetite all day long, but also provide important antidepressant effect.

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'Dexamyl' *Spansule*—daylong control of appetite *plus* psychic support for your dieting patient.





New Hygroton®

brand of chlorthalidone

longest in action... smoothest in effect

in hypertension and edema

potent antihypertensive-saluretic

greater loss of sodium
lesser loss of potassium

A new antihypertensive-saluretic, Hygroton now enables still more effective and safer control of hypertension and edema.

more evenly sustained therapeutic response
Because it has the most prolonged action of all diuretics[1] Hygroton exercises smoother, more evenly sustained therapeutic effect... with almost complete freedom from significant side reactions.[2-4]

more nearly pure natriuretic effect
Hygroton produces only minimal potassium loss[1,5] ...affords a better sodium-potassium ratio than other saluretics.[5]

more liberal diet for the patient
As a rule, with Hygroton restriction of dietary salt is unnecessary.

more convenience and economy
Administration of just three single doses per week, for maintenance therapy, made feasible by the prolonged action of Hygroton,[2] insures maximal convenience and economy.

affording still greater assurance of response

In arterial hypertension
sustained control without side reactions.

In the management of arterial hypertension Hygroton produces significant and sustained fall in blood pressure in 83 per cent of patients without production of autonomic side effects.[6] Comparatively it affords "superior overall clinical effect" to that of other commonly used diuretics.[7]

In edematous states
copious diuresis without electrolyte imbalance.

In edema associated with congestive failure, nephrosis, hepatic cirrhosis, pregnancy or hypercortisonism Hygroton produces a marked salt and water diuresis without significant effect on other electrolytes.[2-5] Edematous swelling, dyspnea, cough and other symptoms are dramatically relieved.

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Bibliography
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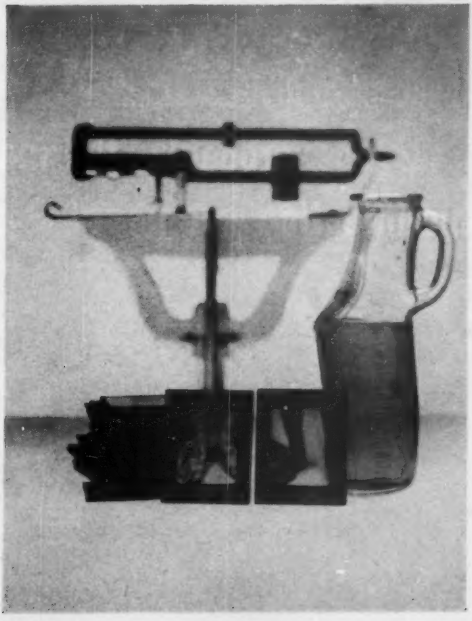
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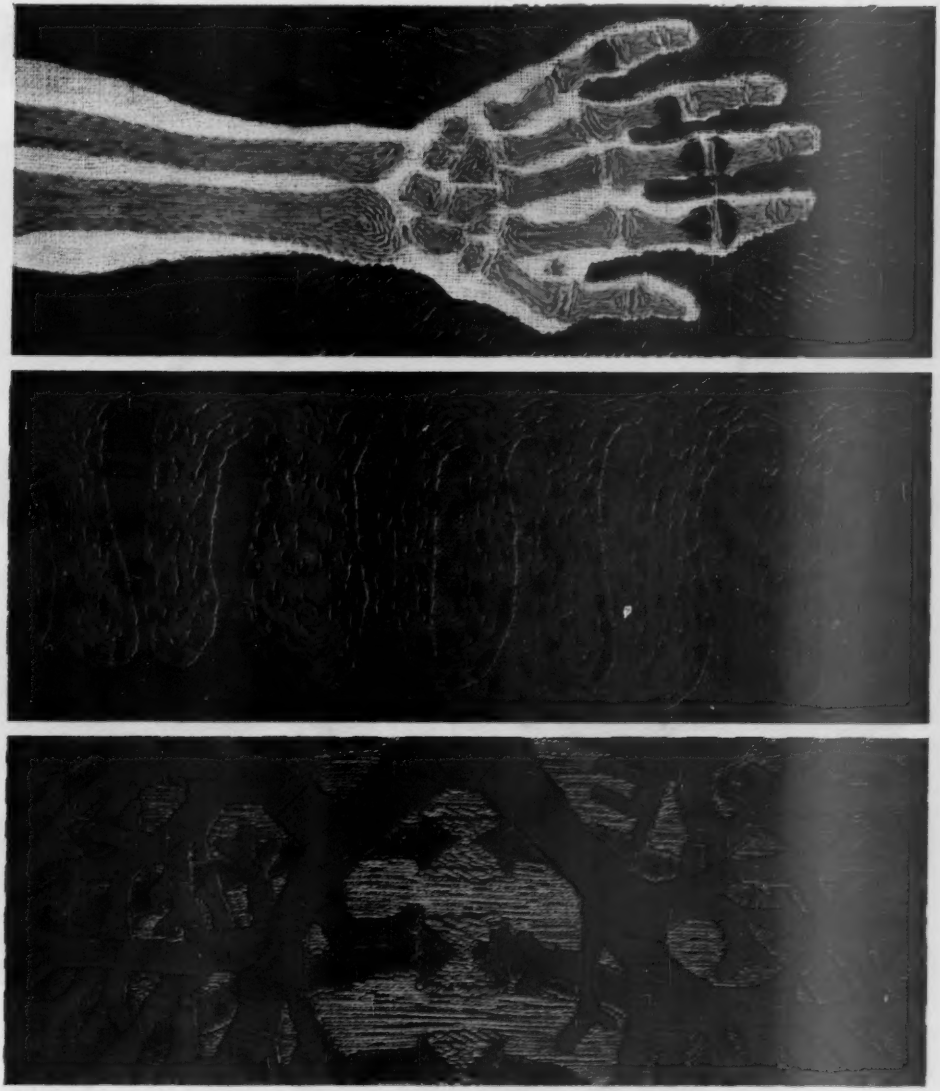
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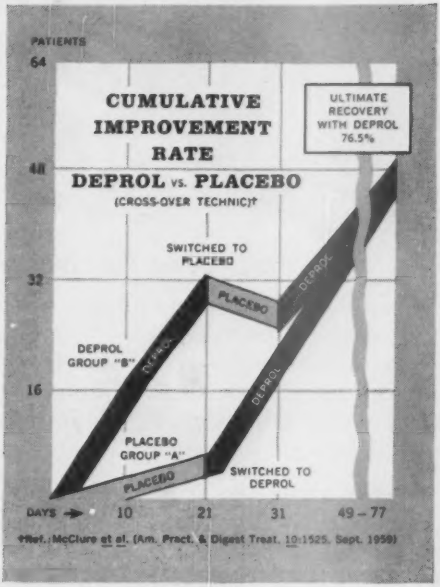
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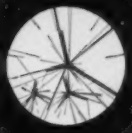
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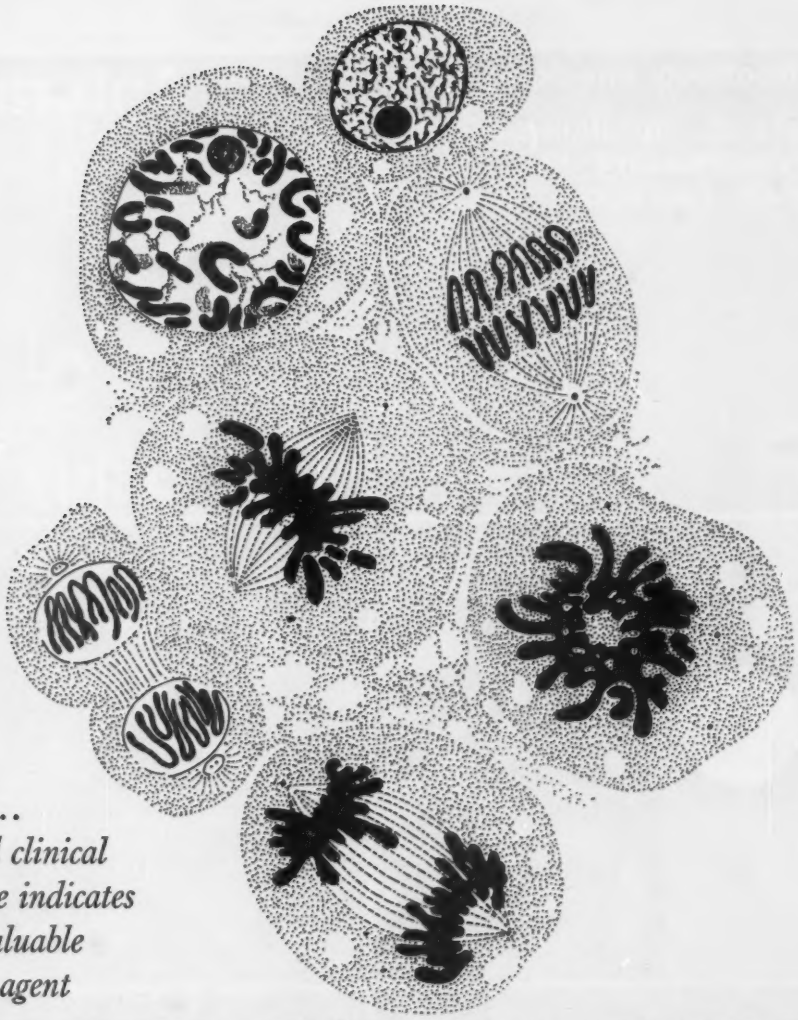
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ANNALS OF
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VOLUME 53 JULY, 1960 NUMBER 1

ADRENOCORTICAL STEROIDS IN THE MANAGEMENT OF *SELECTED* PATIENTS WITH INFECTIOUS DISEASES *

By WESLEY W. SPINK, M.D., F.A.C.P., *Minneapolis, Minnesota*

IT was pointed out in previous reviews on this subject that the judicious use of adrenocorticotropin and the corticosteroids frequently contributed to immediate improvement in the condition of patients seriously ill with infections and their complications.[1, 2] Additional evidence has been widely documented in the literature. That these steroids were potentially dangerous agents and should be administered cautiously was also emphasized. But accumulated clinical experience has not demonstrated serious side-effects, except in rare instances, when the adrenocorticosteroids were used over a brief period of time in critically ill patients. On the contrary, the benefits have far outweighed the hazards. However, many problems remain relating to the conditions under which the steroids should be used in the management of infectious diseases. Apprehension is still expressed over the danger of giving the steroids. More precise information is needed in the human patient relative to the frequency with which the defense mechanism against infection is impeded by the steroids. It is also desirable to know more about the reactivation of latent infections by steroid therapy.

In view of the need for further knowledge on this subject, a summary is presented at this time on studies made between 1950 and 1959 in conjunction with the use of the steroids in 81 selected patients in the clinics of the University of Minnesota Medical Center. A spectrum of results has been observed. At one end they have been definitive and reproducible, with immediate improvement observed in the condition of the patients. At the

* Received for publication December 22, 1959.
Presented at the Seventy-second Annual Meeting of the American Clinical and Climatological Association, Hot Springs, Va., Nov. 4, 1959.
From the Department of Medicine, University of Minnesota Medical School, Minneapolis.
Requests for reprints should be addressed to Wesley W. Spink, M.D., Department of Medicine, University of Minnesota Medical School, Minneapolis 14, Minnesota.

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other end of the therapeutic spectrum, it has not been easy to assay the effect of the steroids on the clinical course of the patients. This applies particularly to the patients with shock due to an infection. It is for this reason that a series of controlled studies on bacterial shock in animals has also been carried out in the laboratory.

Patients Selected for Treatment

The clinical conditions for which the steroids were employed are presented in table 1. The largest group consisted of 38 patients with acute peripheral vascular failure. The majority of these patients with shock had infections due to gram-negative bacteria. The next largest group treated

Table 1

Conditions Under Which Steroids Were Used

Diagnosis	No. of Patients	
1. Shock due to:		
Coliform-Pseudomonas-Proteus bacterial group	25	
Pneumococcus	4	
Meningococcus	2	
Salmonella	2	
Staphylococcus	2	
Lupus erythematosus with sepsis	2	
Clostridia	1	
	—	38
2. Drug reaction		9
3. Infectious mononucleosis with encephalomeningitis or jaundice		6
4. Mumps with encephalomeningitis and/or orchitis		5
5. Brucellosis		5
6. Tuberculosis		5
7. Acute rheumatic fever		3
8. Hepatitis		2
9. Trichinosis		2
10. Pneumococcal meningitis		2
11. Meningococcal meningitis without shock		1
12. Varicella encephalitis		1
13. Subacute bacterial endocarditis		1
14. Eosinophilic pneumonia		1
		81

had severe drug reactions, most of which were the result of antibiotic therapy. The remainder of the patients were seriously ill and suffered from a variety of clinical conditions in which undesirable inflammatory reactions were prominent. The attending staff concurred in the decision to employ the steroids, along with other therapeutic measures, in an attempt to subdue the inflammation.

The basic philosophy underlying the therapy of these patients was the use of pharmacologic doses of adrenal steroids for a period of a few days in critically ill patients. Steroids were often administered in relatively large doses, not because of impaired adrenal function, but because the maximal output of adrenal secretion appeared to be inadequate during a period of severe stress.

Steroid Therapy in Shock Due to Infection

There is probably no area in which further information is more urgently needed than in the problem of patients with peripheral vascular failure due to infection. It has been difficult to evaluate the role of the steroids in the management of this form of vascular collapse, because so little is known about the fundamental nature of bacterial shock. Furthermore, in critically

Table 2

Summary of Patients with Shock Due to Coliform-Pseudomonas-Proteus Group of Organisms

No.	Age	Sex	Primary Condition	Bacteriology	Outcome
1	4	F	Ruptured appendix	Principally *E. coli*	Died
2	28	M	Burns—third degree, 45%	**P. aeruginosa*	Died
3	34	M	Diabetes	**P. aeruginosa*	Recovered
4	54	F	Postoperative (hysterectomy)	**E. coli*	Recovered
5	59	M	Cerebral degeneration; postcatheterization sepsis	**P. aeruginosa*	Died
6	60	F	Postoperative colectomy; pyelonephritis	**E. coli*	Died
7	62	M	Cholelithiasis	**E. coli*	Died
8	63	F	Pyelonephritis; uremia	*A. aerogenes* *E. coli*	Died
9	64	M	Cancer of pancreas	**E. coli*	Died
10	65	M	Prostatic hypertrophy with retention	**E. coli*	Died
11	67	M	Liver biopsy	**E. coli*	Recovered
12	68	M	Cancer of prostate	**A. aerogenes*	Died
13	70	F	Diabetes; pyelonephritis	**E. coli*	Recovered
14	70	F	Cancer of gall-bladder; subphrenic abscess	**E. coli*	Died
15	73	M	Urethral abscess	**E. coli*	Died
16	73	M	Pyelonephritis	**E. coli*	Died
17	74	M	Gangrenous cholecystitis	**Klebsiella*	Died
18	79	M	Suprapubic cystostomy	**P. aeruginosa*	Died
19	82	M	Urethral stricture	**Proteus*	Died
20	83	M	Prostatic hypertrophy with retention	**E. coli*	Died
21	83	M	Volvulus; pyelonephritis	*E. coli* *Proteus*	Died
22	83	M	Prostatic hypertrophy with retention	**A. aerogenes*	Recovered
23	87	M	Arteriosclerotic heart disease and failure; postcatheterization sepsis	**A. aerogenes*	Recovered
24	86	M	Urethral stricture	**Klebsiella*	Recovered
25	87	M	Suprapubic cystostomy	**E. coli*	Recovered

* Present in blood culture.

ill patients with shock a variety of therapeutic procedures is carried out simultaneously, and it is not easy for the clinician to assess the effect of exogenous corticosteroid.

Because the nature of bacterial shock is so poorly understood, and because this type of shock is still a major clinical problem, a series of clinical and laboratory studies has been carried out in this department during the last 10 years. These investigations have been particularly concerned with endotoxin shock.[3-7] The initial studies on patients with shock due to infections with gram-negative bacteria revealed the restricted interpretation that is so often attached to the Waterhouse-Friderichsen syndrome. This

TABLE 3

Age and Sex Distribution of Patients with Shock Due to Coliform-Pseudomonas-Proteus Group

Age (Years)	Sex		Total No.	No. Died
	Males	Females		
Under 30	1	1	2	2
31–40	1	0	1	0
41–50			0	
51–60	1	2	3	1
61–70	5	3	8	7
71–80	4	0	4	4
81–90	7	0	7	3
Total	19	6	25	17

syndrome is frequently looked upon as a condition in which meningococcemia has induced peripheral vascular collapse because of hemorrhage into the adrenal glands and a failure of adrenal cortical secretion. As a matter of fact, the Waterhouse-Friderichsen syndrome is caused by a wide variety of gram-negative and gram-positive microörganisms, and hemorrhage into the adrenal glands severe enough to impair adrenal cortical function rarely occurs. Further experience in these studies showed that the majority of patients having fatal bacterial shock do not have significant morphologic changes in the adrenals. A most fundamental observation was the finding that the secretory activity of the adrenal cortex of patients with shock was excellent, even in moribund patients.[8] In other words, patients dying from endotoxin shock had adrenal glands that responded to stimulation with ACTH as readily as did those of healthy control subjects.

Twenty-five patients with shock due to the coliform-pseudomonas-proteus group of bacteria were investigated and treated with steroids. Pertinent clinical data on these patients are shown in table 2, while table 3 summarizes the sex distribution, age and outcome of the course of the patients. A disturbing feature in this group is that 17 of the 25 patients died.

TABLE 4

Specific Bacteriology and Outcome of Course of Patients with Shock Due to Coliform-Pseudomonas-Proteus Group of Organisms

Bacteriology	Total No.	No. with Bacteremia	No. Died
E. coli	13	12	9
E. coli and *A. aerogenes*	1	0	1
E. coli and *Proteus*	1	0	1
Klebsiella	5	5	2
P. aeruginosa	4	4	3
Proteus	1	1	1
Total	25	22	17

TABLE 5

Therapeutic Procedures in Patients with Acute Bacterial Shock

1. Antibiotics, usually multiple
2. Infusions: whole blood, plasma, water, saline, glucose
3. Pressor agents: norepinephrine and metaraminol
4. Adrenocortical steroids
5. Oxygen

However, it is to be noted that the majority of the patients were well advanced in age. Most of the patients were males, and causative factors were retention of urine, urinary tract infections, catheterization of the bladder, and surgical operations. Bacteriologic data for these patients are given in table 4. There was a preponderance of infections due to *Escherichia coli*.

The various therapeutic procedures utilized in these patients are listed in table 5. All of the patients received broad-spectrum antibiotics and parenteral fluids. Either norepinephrine or metaraminol, or both, were used as pressor agents. It was recognized that, during the initial stages of endotoxin shock, severe vasoconstriction occurs, and during this early stage the pressor drugs could accentuate the generalized vasoconstriction. How-

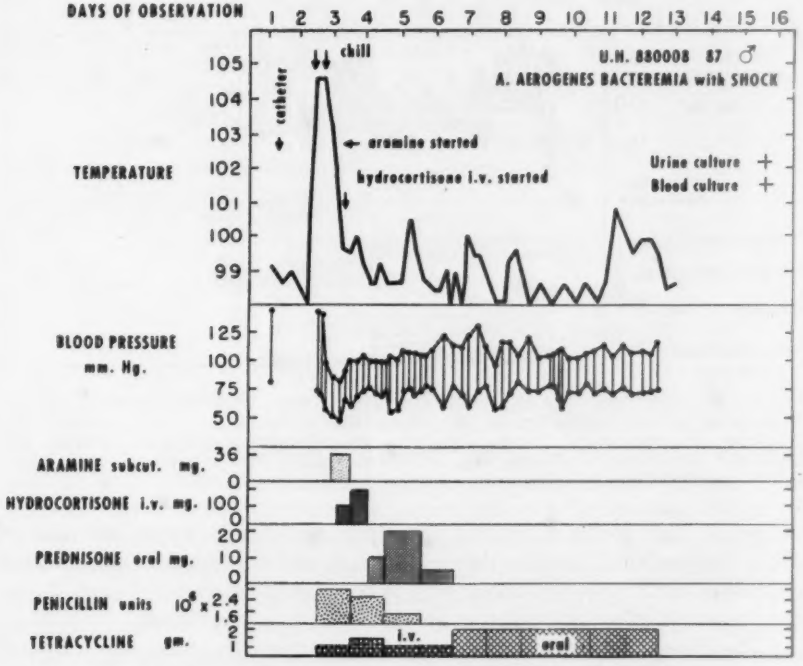


FIG. 1. Clinical course of 87 year old male with bacterial shock due to *Aerobacter aerogenes*. Bacteremia followed catheterization of the urinary bladder. The blood pressure was stabilized with metaraminol (Aramine), and hydrocortisone was administered intravenously. The patient recovered.

ever, experimental studies being readied for publication have shown that the vasoconstriction in endotoxin shock is followed by vasodilation, a decline in blood pressure, and a pooling of blood on the venous side. A reduction of cardiac output takes place. These drugs were administered for the purpose of increasing cardiac output and stabilizing the blood pressure in an attempt to combat the hypoxia. Further investigation also revealed that the severe vasoconstriction induced by the drugs is less likely to occur if the systolic pressure in previously normotensive individuals is maintained around

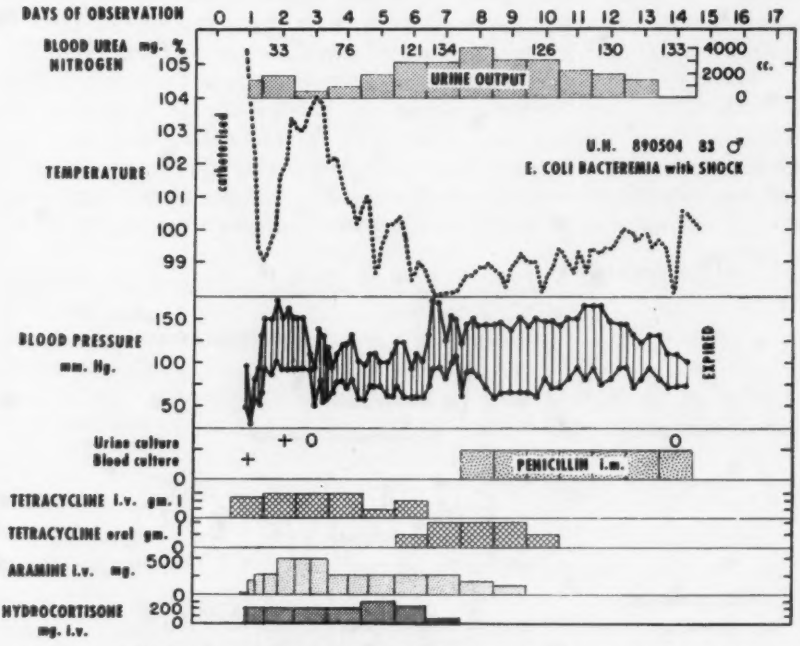


FIG. 2. Clinical course of 83 year old male with bacterial shock due to *Escherichia coli*. Bacteremia followed catheterization of urinary bladder. Also, his blood pressure was stabilized with metaraminol (Aramine) and his general condition improved. Diuresis was associated with a rise in nitrogen retention, and the patient died in uremia. Renal failure in this patient reflects the most serious complication of endotoxin shock.

90 mm. of Hg, and certainly not permitted to rise much above 100 mm. of Hg. Supplemental oxygen therapy appears to be advantageous. Studies on endotoxin shock in the laboratory (to be published elsewhere) have shown the protective effect of oxygen in animals with endotoxin shock.

The course and treatment of representative cases are presented in figures 1 and 2. Figure 1 illustrates the course of an 87 year old male who developed shock shortly after catheterization of the bladder. *Aerobacter aerogenes* was isolated from a blood culture. He was promptly treated with

metaraminol (Aramine), steroids and tetracycline, and recovered. On the other hand, figure 2 shows the course of an 83 year old male who developed profound shock after catheterization and invasion of his blood stream by *E. coli*. Treatment with metaraminol restored his blood pressure, probably at a systolic level which was too high. Although he had a good diuresis, nitrogen retention became more severe, and he died in uremia. Renal failure has been the most serious complication in this group of patients with endotoxin shock.

TABLE 6

Pneumococcal Lobar Pneumonia with Shock

No.	Age	Sex	Pertinent Clinical Features	Treatment	Outcome
1	54	M	R.L.L. and R.M.L. pneumonia Severe alcoholism Severe leukopenia (2,750) Shock (B.P., 80/60)	Penicillin Cortisone (orally) 200 mg. × 1 day 150 mg. × 1 day 100 mg. × 1 day 50 mg. × 1 day 25 mg. × 1 day	Slow convalescence; thrombophlebitis
2	28	M	R.L.L. pneumonia Severe alcoholism Shock (B.P., 85/55)	Penicillin Aramine, 50 mg. I.V. × 1 Cortisol, 100 mg. I.V. × 1	Prompt recovery
3	64	M	Hypertensive arteriosclerotic heart disease with failure. Postmyocardial infarction. Bacteremia, Type III. *D. pneumoniae*. Shock (B.P., 105/0)	Penicillin Digitoxin Aramine, 4 mg. I.V. × 1 Cortisol, 200 mg. I.V. × 1	Recovery
4	40	M	R.U.L. pneumonia Shock after initial penicillin. Bacteremia, *D. pneumoniae*. Shock (B.P., 80/60). No benefit from Aramine.	Penicillin Tetracycline Aramine, 40 mg. S.C. × 2 Cortisone (orally) 150 mg. × 2 days 75 mg. × 1 day 50 mg. × 1 day 25 mg. × 1 day 2.5 mg. × 2 days	Recovery

Although the mortality rate in this group of treated patients was high and the evaluation of steroid therapy difficult, the clinical staff concluded that recovery of some of the patients was related to intensive steroid therapy. In the light of subsequent experience, it is not unlikely that the dose of steroid used in some patients was inadequate. Large doses of steroid given by an intravenous route should be employed in the early stages of treatment. The present policy is to give 300 to 500 mg. of hydrocortisone, or its equivalent, every eight to 12 hours for two to three days. No harmful effects have been observed with this régime.

The use of large doses of steroid in human patients has been derived in part from studies on experimental shock in dogs following the administration

of lethal injections of endotoxin. It has been shown (in experiments to be published elsewhere) that hydrocortisone administered *after* the development of shock will prolong life and modify the severity of the hemorrhage and edema of the gastrointestinal tract, which is a prominent feature of endotoxin shock in the dog. Tissue injury in canine endotoxin shock is reflected in markedly elevated titers of the serum-glutamic-oxalacetic-trans-

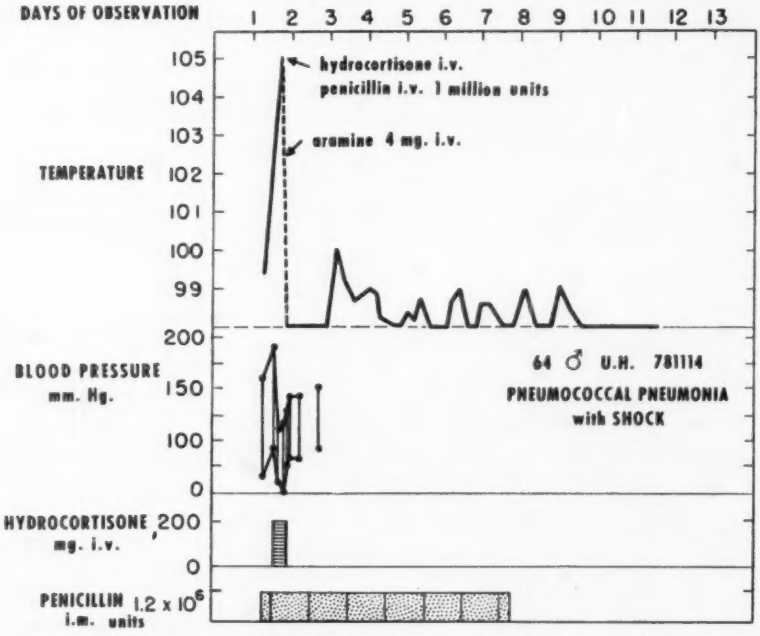


FIG. 3. Clinical course of 64 year old male with lobar pneumonia and bacteremia due to Type III *Diplococcus pneumoniae*. The patient had hypertensive arteriosclerotic heart disease with evidence of a previous myocardial infarction. He responded favorably to treatment which included hydrocortisone and metaraminol.

aminase (SGOT). However, when large doses of hydrocortisone were infused, tissue injury was mild, and the activity of SGOT was considerably reduced.[9]

The influence of steroid therapy on the course of bacterial shock was more apparent in a group of four patients who had vascular collapse in association with pneumococcal lobar pneumonia. Clinical data on these patients are shown in table 6. All four patients recovered, and it was concluded that the administration of adrenocortical steroids contributed to their recovery. This was particularly obvious in case 3 (table 6), a 64 year old white male with lobar pneumonia and bacteremia due to Type III pneumococci. He also had congestive heart failure, with a history and electro-

cardiographic evidence of an old posterior myocardial infarction. His clinical course is illustrated in figure 3. The temperature was 105° F. He appeared to be cyanotic and extremely toxic. After a single intravenous injection of 200 mg. of hydrocortisone the toxicity abated and the fever subsided. His blood pressure was stabilized following an intravenous infusion of 4 mg. of metaraminol. The favorable influence of hydrocortisone in pneumococcal pneumonia with bacteremia and shock was equally clear-cut

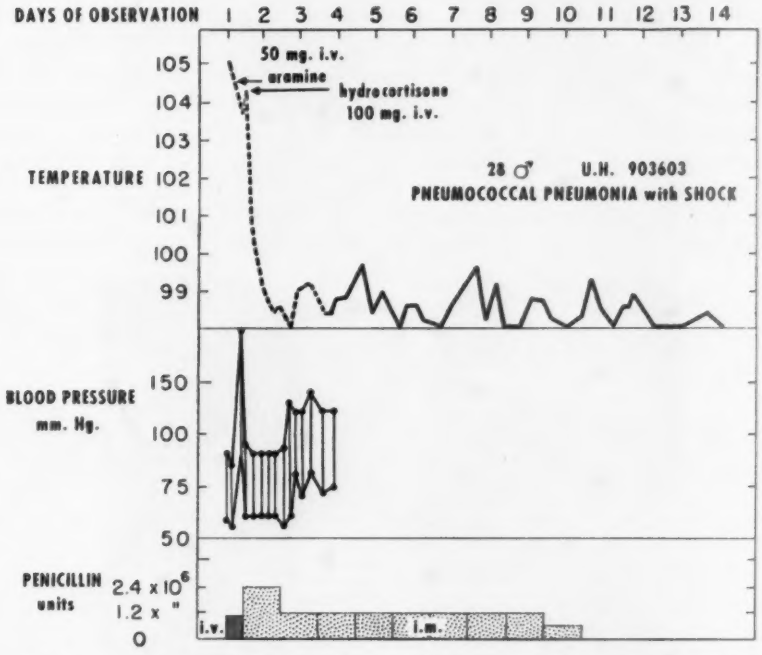


FIG. 4. Clinical course of 28 year old male who was an alcoholic and was critically ill with pneumococcal lobar pneumonia and bacteremia. He had severe shock, and the blood pressure was not raised after a large intravenous dose of Aramine. However, his pressure was elevated and his condition improved immediately following a single intravenous injection of hydrocortisone.

in case 2 (table 6), a 28 year old alcoholic male. His course is shown in figure 4. His temperature was 105° F., and *following* an intravenous injection of penicillin, vascular collapse developed. His condition rapidly became critical. An infusion of a large dose of metaraminol did not stabilize his blood pressure. His pressure was stabilized only after the intravenous administration of 100 mg. of hydrocortisone. In addition, the fever abated, and his condition rapidly improved.

The outcome of the course of 38 patients with bacterial shock is presented

TABLE 7

Outcome of Course of Patients with Bacterial Shock

Bacteriology	No. of Patients	
	Recovered	Died
Coliform-Pseudomonas-Proteus group	8	17
Pneumococcus	4	0
Meningococcus	1	1
Salmonella	0	1
Staphylococcus	0	2
Lupus erythematosus with shock	2	1
Clostridia perfringens	0	1
Total	15	23

in table 7. Twenty-three of the patients died, yielding a mortality rate of 60%. It is of interest that there were two children with meningococcal infections and shock. One patient recovered. The fatal case was the only instance of hemorrhage of the adrenals seen in this study. Steroid therapy did not appear to alter the course of the remaining patients, with one exception, a 48 year old housewife with severe rheumatic arthritis and lupus erythematosus. She was first seen in 1950, and at that time steroid therapy

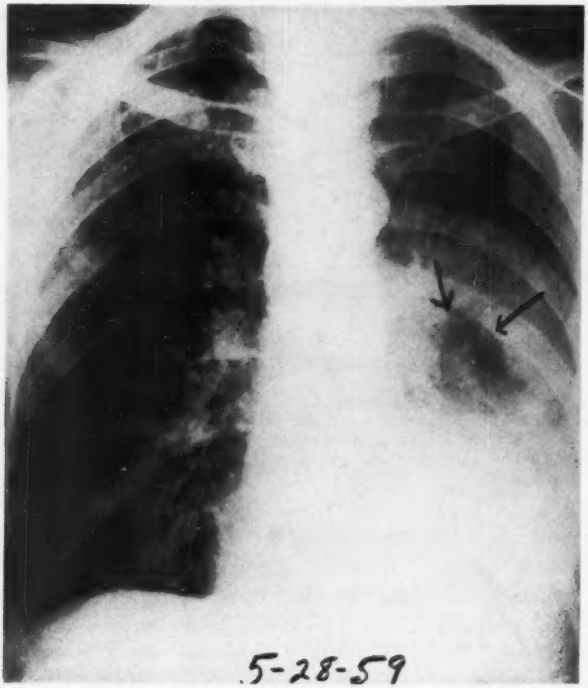


FIG. 5. Acute pulmonary abscess in 48 year old female with lupus erythematosus and peripheral vascular collapse. Her blood pressure was stabilized and her condition improved immediately after an intravenous infusion of 300 mg. of hydrocortisone.

was contemplated, but because of a previous history of pleural effusion with a residual calcified area in the lung, some apprehension was expressed over reactivating a latent tuberculosis. After a lapse of years she entered the hospital in 1959 in a moribund state. She had severe rheumatoid arthritis and hematologic evidence of lupus erythematosus. She manifested cyanosis, severe toxicity, vascular collapse, and evidence of an extensive pulmonary

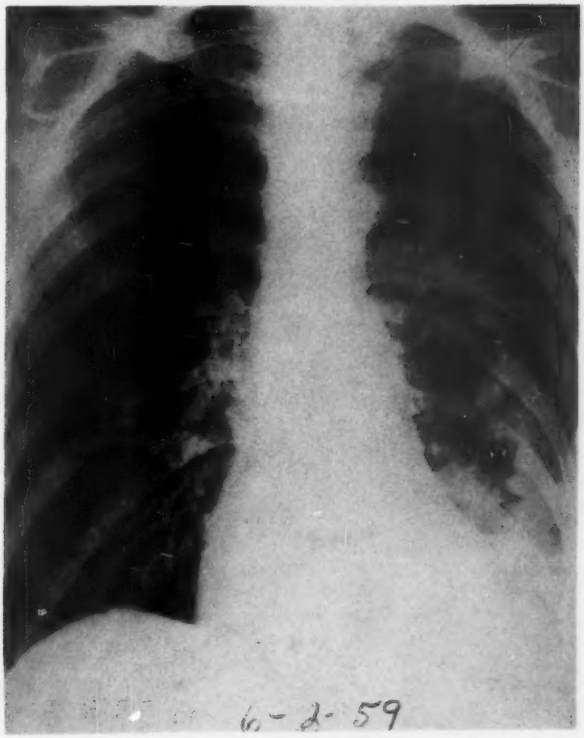


FIG. 6. Improvement in pulmonary condition of foregoing patient five days after receiving hydrocortisone and antibiotics.

abscess of the left lower lobe (figure 5). Whole blood transfusions, oxygen and antibiotics were administered, but her condition continued to deteriorate. She was then given 300 mg. of hydrocortisone intravenously. This dose was given every eight hours for a total of three doses, and then prednisone was administered orally. She was not given a pressor drug. Within a few hours after receiving the first dose of hydrocortisone she improved, and continued to do so in a remarkable manner. Figure 6 is an x-ray of the chest taken five days after the first, and figure 7 shows the pulmonary condition 57 days after entry into the hospital. There is no question that

steroid therapy resulted in rapid improvement of a desperately ill person. After she had recovered, an ACTH test revealed normal adrenal cortical function.

In summary, studies on bacterial shock carried out in this clinic during the last 10 years have revealed that definitive therapy remains unsatisfactory, largely because the mechanisms involved in the pathogenesis of peripheral vascular collapse are not understood. The mortality rate in the aged remains high. Experimental and clinical studies indicate that the parenteral

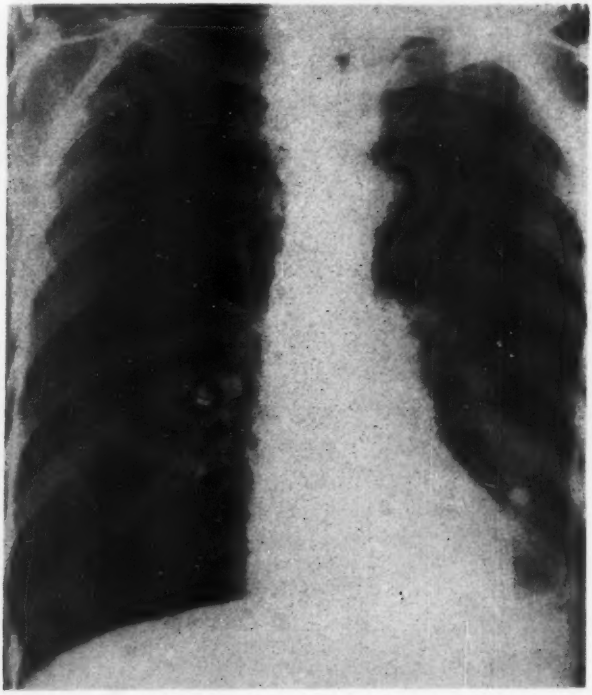


FIG. 7. Continued improvement manifested in lung of patient 57 days after initial x-ray, shown in figure 5.

use of large doses of adrenal cortical steroid given over a period of a few days is not harmful, and has contributed to the improvement and recovery of some patients.

ADRENOCORTICAL STEROIDS FOR UNDESIRABLE INFLAMMATORY REACTIONS IN INFECTIOUS DISEASES

Inflammation is an essential factor in the defense mechanism against infections. But inflammatory reactions can be harmful to the host, and often unnecessary. It is becoming more and more obvious that inflamma-

tion appearing during the course of an infectious disease frequently represents a delayed type of acquired microbial hypersensitivity. This applies particularly to a disease like tuberculosis. Inflammation can be especially harmful when certain organs are involved, such as the heart, or when the central nervous system is the site of reaction. Sufficient evidence is now available showing that certain inflammatory states occurring in the course of infections can and should be promptly subdued. At present, the adrenocortical steroids are the most efficient agents for this purpose.

TABLE 8

Patients with Infectious Mononucleosis Treated with ACTH or Adrenocortical Steroids

No.	Age	Sex	Pertinent Clinical Features	Treatment	Outcome
1	21	M	Fever (105° F.); ill 2 wks. with severe vomiting and headache	ACTH, 25 units I.M. q. 6 hrs. for 5 days	Dramatic improvement; recovery
2	21	M	Fever, chills, severe headache, with increased CSF pressure and lymphocytosis; lymphadenopathy	ACTH, 40 units I.V. daily × 2	Marked improvement; recovery
3	23	M	Ill 2 wks. with severe toxicity, headache, fever, chills; lymphadenopathy	ACTH, 100 units × 1 day I.M., 80 units × 2 days 60 units × 1 day 40 units × 1 day 30 units × 1 day 10 units × 1 day	Marked improvement immediately; recovered
4	22	F	Fever, lethargy; lymphadenopathy	9α-fluorohydrocortisone (orally), 2 mg. b.i.d. × 3	Prompt improvement; recovery
5	19	F	Fever, severe pharyngitis, headache, vomiting; lymphadenopathy	Cortisone, 25 mg. 4 × daily × 3 days (orally)	Prompt improvement; recovered
6	19	F	Fever, severe pharyngitis, jaundice; lymphadenopathy	ACTH, 40 units I.V. × 1 20 units daily × 5	Prompt decline in fever; sore throat persisted; improvement gradual

Infectious Mononucleosis: Studies on unselected patients with infectious mononucleosis revealed that steroid therapy did not alter the clinical course favorably enough to warrant the use of these agents in this disease except when certain complications appeared, such as inflammation involving the central nervous system.

Table 8 shows the essential data on six patients with severe illness due to infectious mononucleosis who were given steroids. Since several of these individuals were treated during the initial phases of this study, ACTH was employed. At present, hydrocortisone or one of the analogues would be selected instead of the agents that were used in these patients. Nevertheless, improvement was prompt in each of the first five patients shown in

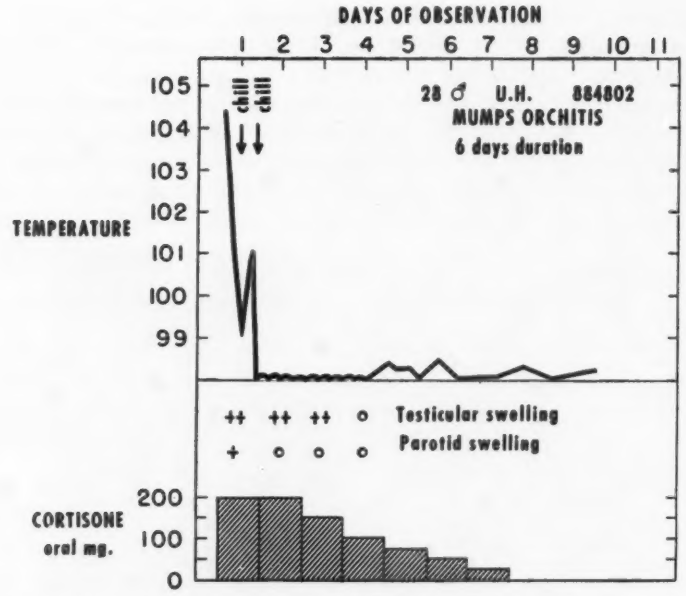


FIG. 8. Typical response to cortisone in 28 year old patient with orchitis due to mumps. Dose of steroid gradually reduced over a period of a week.

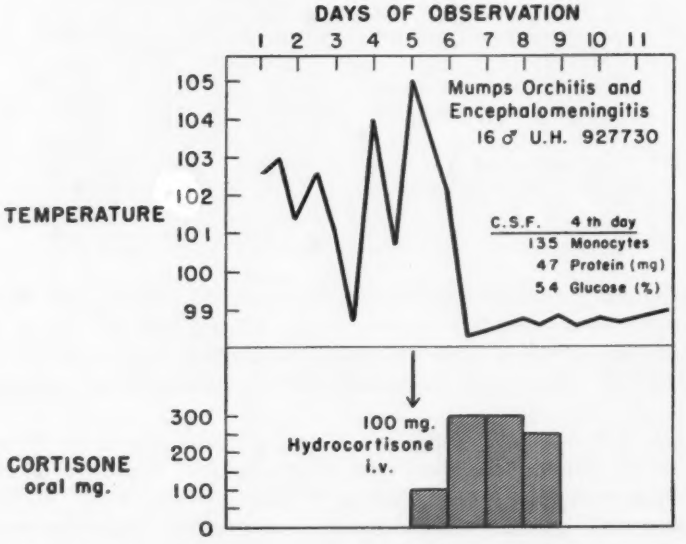


FIG. 9. Illustrating the prompt improvement following treatment with hydrocortisone in a 16 year old male seriously ill with orchitis and encephalomeningitis due to mumps.

table 8. They had evidence of encephalomeningitis, and relief of the headaches, lethargy and toxicity was remarkable. Case 6 had severe pharyngitis and jaundice, but gradually improved with ACTH therapy.

Mumps: Steroid therapy should be considered in selected patients with the complications of mumps. Such treatment is not recommended routinely for patients with orchitis, but should be reserved for individuals in a febrile and toxic state and with a painful effusion into the scrotal sac. Under these conditions the steroids may afford relief of pain and a diminution in inflammation. Two patients with orchitis were selected for treatment, one of whom had an associated encephalomeningitis. The response in one patient with orchitis who was treated with cortisone is shown in figure 8.

TABLE 9

Patients Having Tuberculosis and Given Steroids

No.	Age	Sex	Pertinent Clinical Features	Treatment	Outcome
1	52	M	Pulmonary and renal tbc. in May, 1956. Treated at sanatorium; improved, with 3 neg. sputa. Fistula-in-ano, extremely painful. Sept., 1956, saucerization of rectal ulcer; postoperative shock and pulmonary infiltrate.	Initially, SM, PAS, INH. For postoperative shock Aramine and Cortisol (figure 10)	Some improvement with Aramine; prompt and progressive improvement with Cortisol
2	42	M	Discoid lupus treated with Cortisol. Past history of tbc. Wife and child died of tbc. Tbc. reactivated; sputa positive. Also developed meningitis.	SM, PAS and INH	Improved; recovery
3	44	M (Indian)	Acute miliary tbc. with severe purpura and thrombocytopenia and leukopenia. Caseation and necrosis in sternal bone marrow, with acid-fast organisms present.	SM, PAS and INH with no improvement; fever and purpura persisted. Cortisol given, with dramatic improvement (figure 17)	Recovery
4	67	M	Acute Bell's palsy; pulmonary tbc. with effusion 6 years previously; cancer of prostate.	Medrol, 10 mg. b.i.d. × 10 days; SM, PAS and INH	No improvement of Bell's palsy
5	81	M	Pulmonary tbc.; acute myelogenous leukemia appeared after initiating antibiotic therapy; purpura	PAS, INH, tetracycline; prednisone orally, 40 mg. daily × 11 days	Improved

A second patient was critically ill with parotitis, orchitis and encephalomeningitis. He was under observation for four days, during which time his condition remained serious. On the fifth day (figure 9), hydrocortisone was administered intravenously, and then cortisone was given orally. Improvement occurred promptly, within 12 hours after beginning treatment, his temperature declining from 105° F. to 98.6° F.

Thrombopenic purpura is a rare but serious complication of mumps. Three adults with this complication were definitely improved after receiving ACTH, cortisone and prednisone, respectively. The clinical features relating to these patients have been reported elsewhere.[10]

Tuberculosis: A large body of information has been recorded in the literature on the use of the adrenocortical steroids in tuberculosis. If one reviews these data, three significant features emerge. First, surprisingly few cases of latent human tuberculosis have been reactivated as a result of

steroid therapy. Second, the dissemination of active tuberculosis, even without the simultaneous use of antituberculosis drugs, rarely occurs. Third, there are now clear indications for the use of the steroids in the management of selected cases of tuberculosis, in conjunction with antituberculosis agents.

It is not the present purpose to review the extensive literature on this subject, but rather to record the experience with steroids in five selected patients who had tuberculosis. Pertinent data relating to these patients

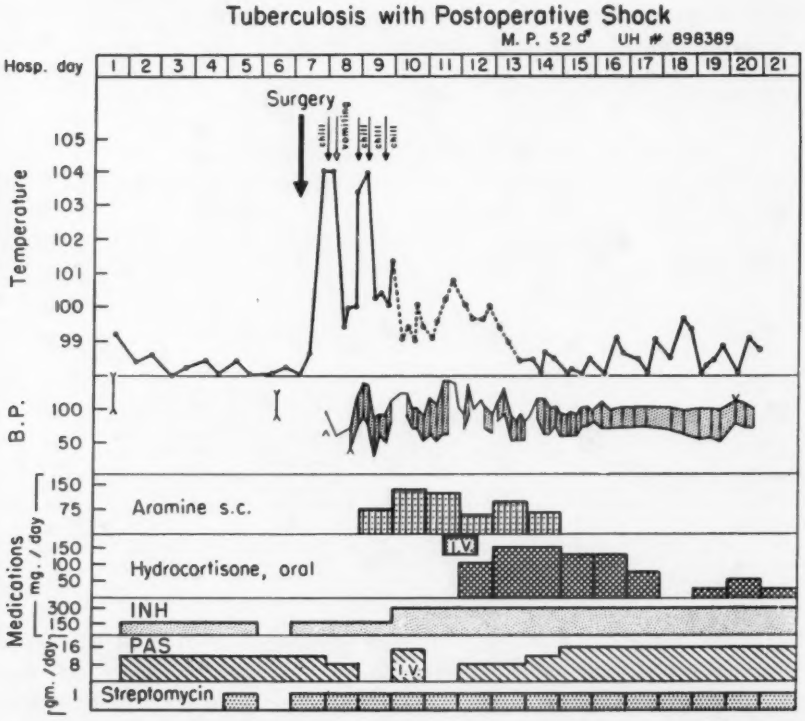


FIG. 10. Clinical course of 52 year old white male being treated for extensive pulmonary and renal tuberculosis who developed shock after excision of a rectal ulcer. The patient was critically ill. Immediate improvement took place after the administration of hydrocortisone.

are given in table 9. Attention is focused especially on two of these patients (cases 1 and 3, table 9), since steroid therapy was life-saving in each instance. Case 1 entered the University Hospitals in May, 1956, because of diffuse pulmonary tuberculosis and renal tuberculosis. He was treated thereafter in a sanatorium over a period of four months with antituberculosis drugs. An exquisitely painful rectal ulcer, probably of tuberculous origin, necessitated reëntry into the University Hospitals. Because of the intense

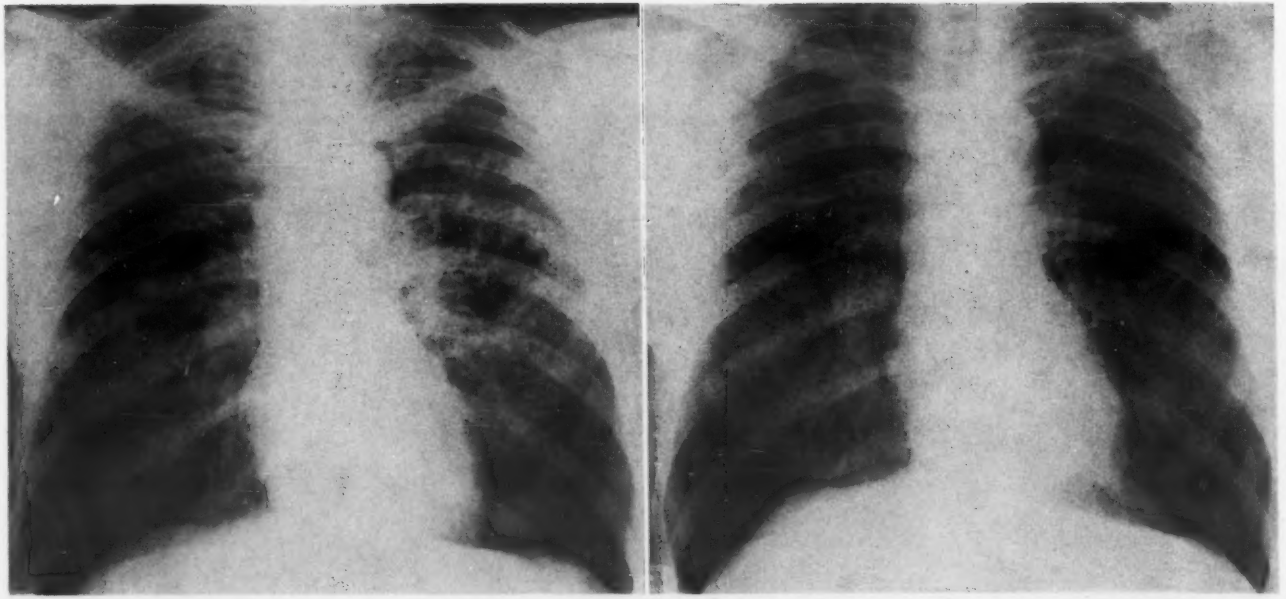


FIG. 11. FIG. 12.

FIG. 11. May 9, 1956. Bilateral pulmonary infiltrate of tuberculous origin before patient referred to in figure 10 had antituberculosis therapy.

FIG. 12. September 24, 1956. Marked improvement in lungs after four months of therapy of patient whose course is illustrated in figure 10.

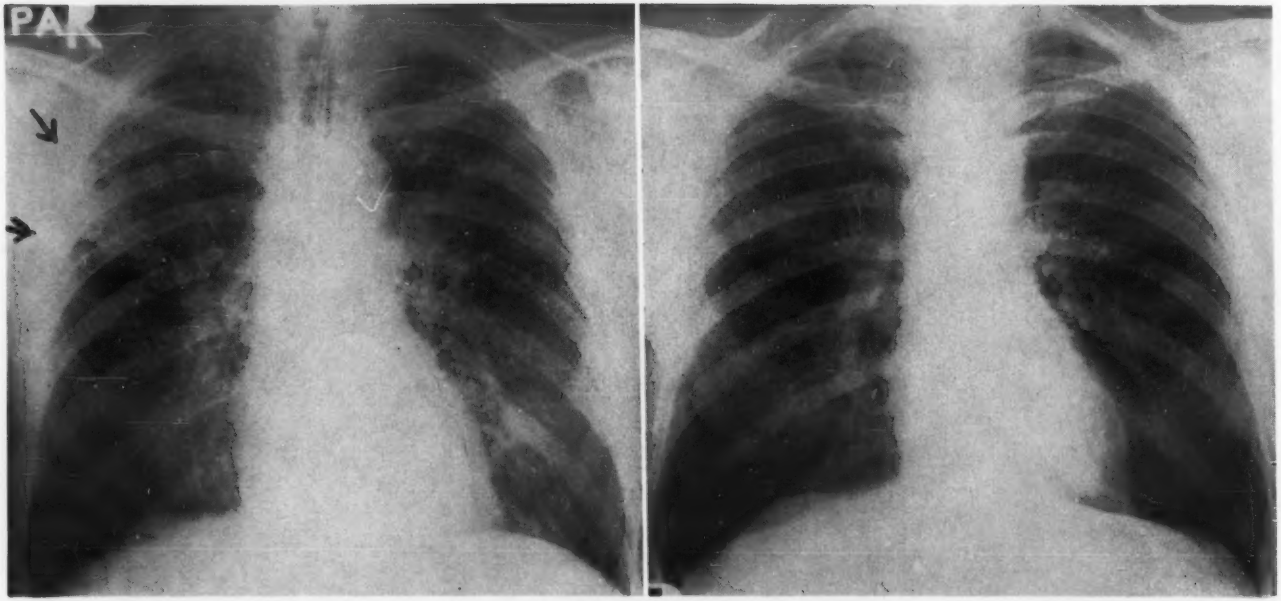


FIG. 13. FIG. 14.

FIG. 13. October 1, 1956. Diffuse pulmonary infiltrate in patient referred to in figure 10 shortly after the excision of a rectal ulcer, probably of tuberculous origin.

FIG. 14. October 10, 1956. Rapid clearing of lung fields in patient described in figure 10 after administration of steroids.

pain, the surgical consultants concluded that excision of the ulcer was necessary. Immediately following surgery the patient developed peripheral vascular collapse and a diffuse pulmonary infiltration. It became apparent during the early phases of his shock that the pulmonary infiltration was not the result of cardiac failure. He became febrile and toxic. It was then concluded that the excision of a tuberculous ulcer had resulted in the local liberation of tuberculous antigen in a hypersensitive individual, which resulted in anaphylactic shock. The presence of renal tuberculosis suggested that he might have some adrenal insufficiency, but a subsequent ACTH

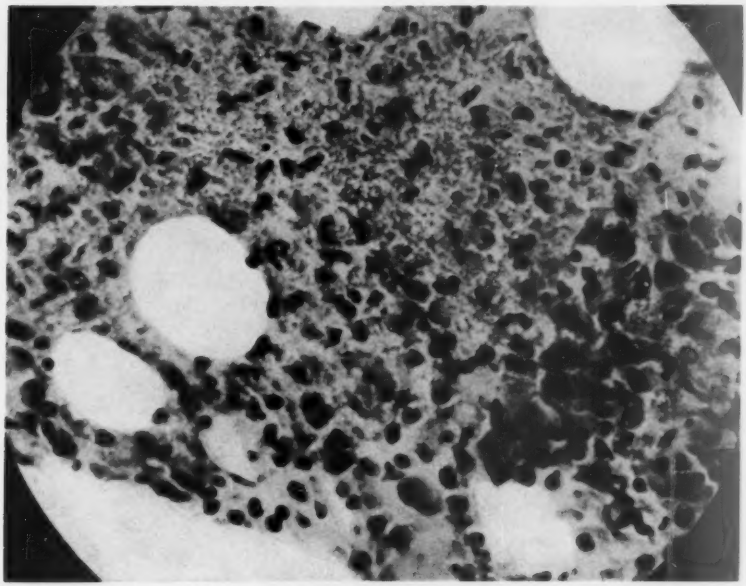


FIG. 15. Aspirated sternal bone marrow from case 3 in table 9, showing necrosis due to tuberculosis. × 700.

test revealed normal adrenal function. While in a state of shock he was given a pressor agent to maintain his blood pressure, but his condition remained critical. Prompt improvement occurred only after the administration of hydrocortisone (Cortisol). The course of this patient is depicted in figure 10. Since this complication is rather unusual, it is of interest to review the x-ray films of the chest in this patient. Figure 11 shows the bilateral pulmonary infiltrate in May, 1956, before antituberculosis therapy. Figure 12 reveals improvement of the lungs after four months of therapy. Figure 13 shows the pulmonary infiltrate immediately after surgical excision of the rectal ulcer, and figure 14 demonstrates clear lungs nine days after surgery, and after steroid had been given.

The second patient with tuberculosis benefited by steroid therapy was case 3, table 9. He was a 44 year old Indian male, seriously ill with acute miliary tuberculosis and thrombopenic purpura. He was febrile and toxic, and was bleeding into the skin, mouth and rectum. Aspirated sternal bone marrow showed necrosis (figure 15) and giant cells (figure 16); a Ziehl-Neelsen preparation (figure 17) revealed an abundance of tubercle bacilli. His condition was critical, and blood transfusions were necessary. He was given antituberculosis therapy in the form of para-aminosalicylate, isoniazid and streptomycin, but he continued to deteriorate, and after 10 days of

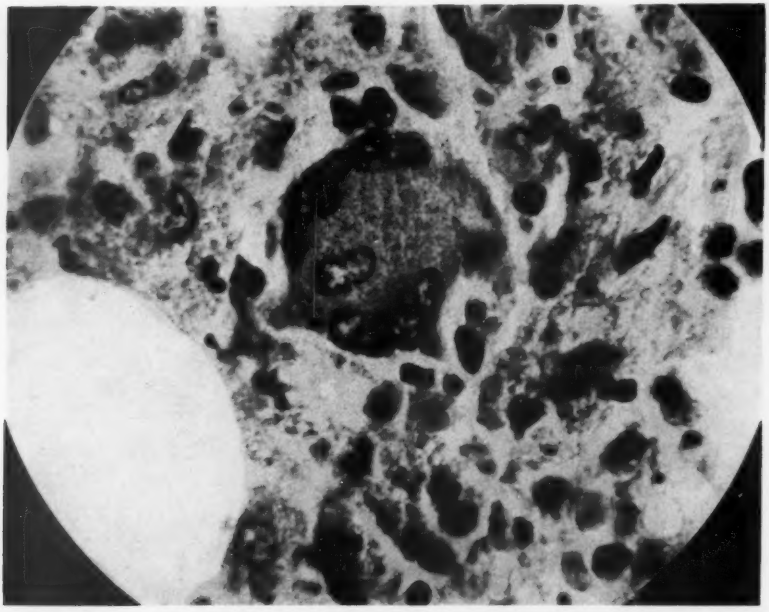


FIG. 16. Aspirated sternal bone marrow from case 3 in table 9, showing giant cell due to tuberculosis. × 1100.

therapy hydrocortisone was administered by mouth (figure 18). He improved within 24 hours, the fever abating and the bleeding subsiding. Although he no longer continued to have purpura, the thrombopenia persisted. When the steroid therapy was discontinued there was no recurrence of bleeding. He continued to improve, and two years later he was well and back at work as a truck driver.

Three other patients illustrate in a different manner the host-parasite balance in tuberculosis and its relation to steroid therapy. Two patients with a past history of tuberculosis were treated with corticosteroids for a condition other than tuberculosis, and at a time when the disease was inactive. Case 2, table 9, had discoid lupus erythematosus. He was

treated elsewhere with hydrocortisone, and without prophylactic antituberculosis agents. His tuberculosis was reactivated and he developed meningitis, but prompt antituberculosis therapy brought about a favorable recovery. Case 4 had an acute Bell's palsy, which disturbed the patient considerably. Obtaining no relief from the usual procedures, he was treated with methylprednisolone. He had had tuberculosis, and was therefore given antituberculosis therapy. The steroid treatment for the Bell's palsy was ineffective; reactivation of the tuberculosis did not occur. Finally, case 5 presented with a complication of tuberculosis that has perplexed physicians

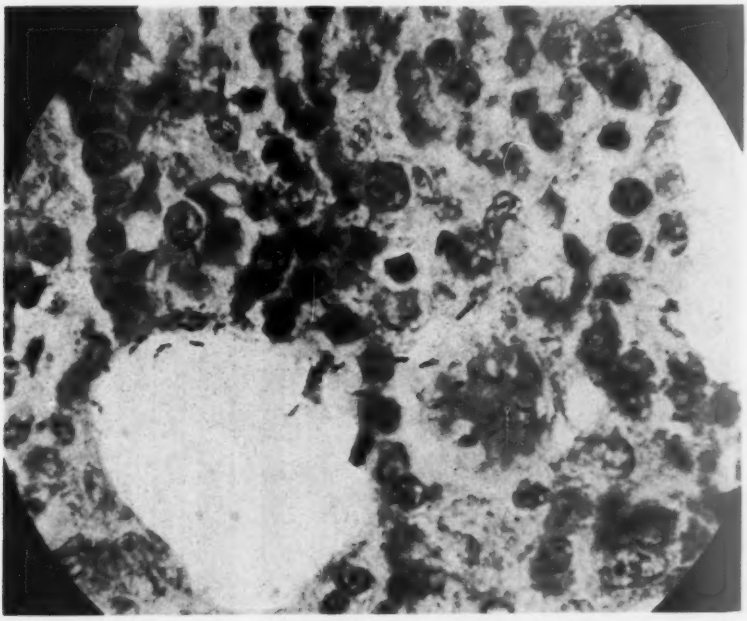


FIG. 17. Aspirated sternal bone marrow from case 3 in table 9, showing *Mycobacterium tuberculosis*. × 1125.

for a long time. Active pulmonary tuberculosis was discovered in a lumberjack who was 81 years of age. Although a normal leukocyte picture was reported at the beginning of antituberculosis chemotherapy, two months following the institution of treatment an acute myelogenous leukemia was detected. Prednisone was administered in an unsuccessful attempt to alter the hematologic condition.

Brucellosis: In many respects the pathogenesis of the illness caused by brucellae is similar to that of tuberculosis. In both conditions the toxicity and inflammation can be partly related to the appearance of acquired hypersensitivity to the invading microörganisms. This aspect of brucellosis has

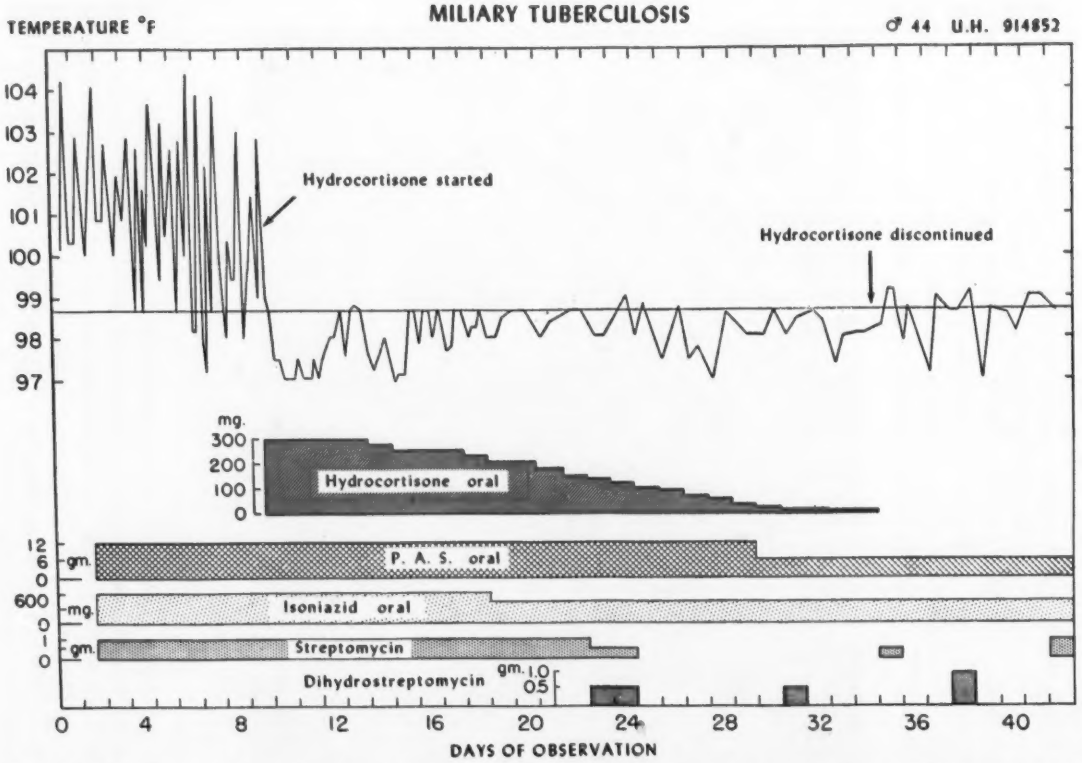


FIG. 18. Clinical course of patient with disseminated tuberculosis (case 3, table 9) who had thrombopenia and severe purpura that did not respond to antituberculosis therapy. Note the prompt response to hydrocortisone.

been extensively studied in this clinic.[11, 12] When an appropriate antibiotic, such as tetracycline, was administered to a febrile patient with acute brucellosis, the temperature and toxemia subsided slowly over a period of a week to 10 days. However, when ACTH alone was given to a patient seriously ill with brucellosis, the temperature subsided within 12 hours, and the patient was greatly improved within 24 hours, although the bacteremia persisted.[13]

The influence of prednisone on the clinical course of a patient with acute brucellosis is shown in figure 19. It will be noted that the steroid was given for three days prior to starting antibiotic therapy. Coincident with admin-

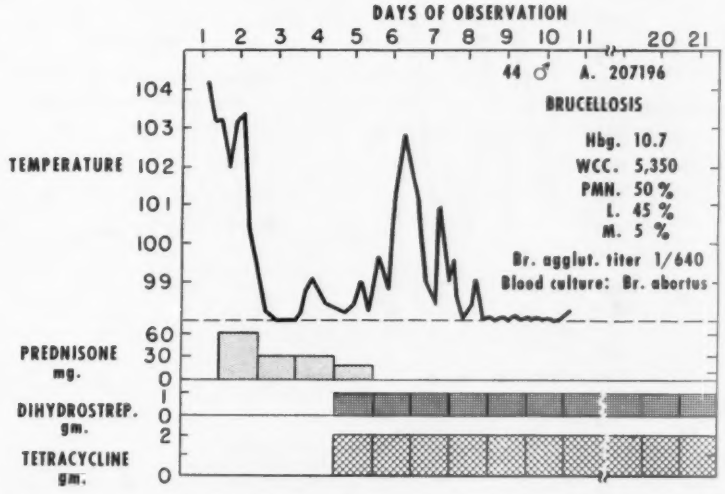


FIG. 19. Clinical course of patient with severe acute brucellosis due to *Brucella abortus*. The administration of prednisone was followed by a prompt drop in temperature and improvement. There was a relapse of his fever when steroid therapy was discontinued and while the patient was receiving antibiotic therapy.

istration of steroid there was a prompt drop in temperature, and the patient felt much better. But when prednisone therapy was discontinued and antibiotics were given, there was a rise in temperature and the patient did not feel so well. Figure 20 shows the clinical course in another patient with acute brucellosis who was given prednisone *simultaneously* with antibiotics. This patient improved rapidly and, except for one slight rise in temperature, remained afebrile and had an uncomplicated recovery.

Because the toxicity in a patient seriously ill with acute brucellosis can be eliminated so rapidly with steroids, five patients have been treated simultaneously with steroid and antibiotics. The results were uniformly favorable. The World Health Organization Expert Committee on Brucellosis

now advises the simultaneous use of steroids and antibiotics in selected patients with brucellosis.[14]

Acute Rheumatic Fever: Although many clinics have used ACTH and the adrenocortical steroids in the management of patients with acute rheumatic fever, it is still not clear whether these agents contribute favorably to the ultimate outcome of the disease in most of the patients. It is generally agreed, however, that the steroids are beneficial in selected patients during a critical phase of their acute illness, when inflammation is such a prominent and debilitating feature. The steroids have proved most useful in those

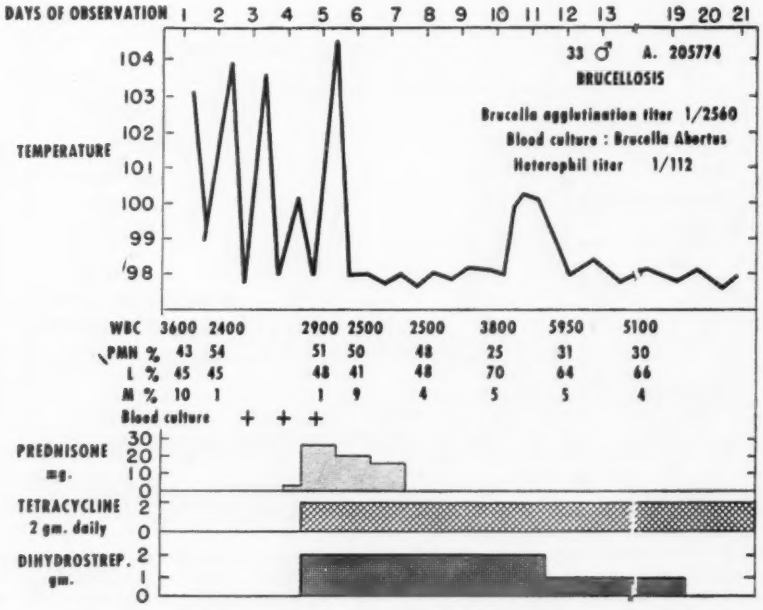


FIG. 20. Clinical course of a patient with severe acute brucellosis due to *B. abortus*. Prednisone was given simultaneously with antibiotics. The fever subsided promptly, and there was rapid improvement in his condition.

patients with pancarditis, or in those with a pericardial effusion in whom salicylates and other similar agents have failed to result in improvement. Patients have exhibited rapid recovery when the steroids have been employed. An unfavorable aspect is that treatment sometimes has had to be given for prolonged periods of time, because relapses have occurred when the dose of drugs was reduced, or omitted entirely.

In the present study, three young patients with severe acute rheumatic fever were selected for treatment. Two had pancarditis with congestive failure. Both recovered eventually, but treatment was prolonged. The

third patient was critically ill with pericarditis and an effusion. ACTH was then administered. He responded favorably, and made a complete recovery without any demonstrable residual cardiac damage.

Hepatitis: The steroids have not been employed routinely in this clinic for acute hepatitis of viral origin. They have been reserved for critically ill patients who were anorectic and who had impending hepatic coma. Two such patients selected for treatment steadily improved thereafter, and eventually recovered. One of these had a history of tuberculosis.

Trichinosis: This is a disease in which acquired hypersensitivity to the parasite *Trichinella spiralis* undoubtedly contributes to illness. Since no specific therapy was available, it appeared reasonable to several investigators to try ACTH or the adrenocortical steroids in the treatment of trichinosis. Prompt improvement followed such attempts. Two patients, included in the present study, were seriously ill with trichinosis, and the use of ACTH and cortisone resulted in immediate improvement.

Pneumococcal Meningitis: This form of suppurative meningitis still remains a serious disease with a significant mortality rate, especially in adults. In a review of 57 cases occurring at the University of Minnesota Hospitals during the penicillin era—that is, between January 1, 1945, and June 30, 1959—the over-all mortality rate was 25%. But the death rate for patients over 40 years of age was 53%. Not only is this mortality rate discouraging, but serious residual complications are also not uncommon. Therefore, any procedure or adjunct in therapy that will reduce the mortality rate and decrease the incidence of complications is highly desirable. The favorable report of Ribble and Braude,[15] in which ACTH and the adrenal steroids, along with penicillin, were employed in the therapy of pneumococcal meningitis in adults, has prompted the addition of steroids in the treatment of this form of meningitis in this clinic. Thus far, only two adults have received this combined treatment, and both died. Further evaluation, however, is under way.

Miscellaneous Infections: There remain diseases in which the steroids were used in only a few cases. There is no indication for the routine use of steroids in patients with uncomplicated *meningococcal meningitis,* because of the excellent results obtained with chemotherapy. But there are two general conditions in which the steroids should probably be employed in the management of this type of suppurative meningitis. First, supplemental steroids should be used in those individuals with peripheral vascular failure; second, treatment with steroids should be seriously considered in those toxic patients critically ill with the manifestations of purpura. The latter group of patients may suddenly develop shock, even though properly selected antibacterial drugs are being given. One child in the second category was critically ill and recovered following the use of chemotherapy and steroids.

One patient with *varicella encephalitis* received steroids, without benefit. Although there are sporadic reports on the use of the steroids in *subacute*

bacterial endocarditis, along with the antibiotics, only one patient in this clinic has been treated in this manner. The result was most favorable. Penicillin was clearly the drug of choice for the disease, but the patient was sensitive to this antibiotic. Therefore, cortisone and penicillin were successfully given simultaneously to the patient. One patient with an unusual and severe *idiopathic eosinophilic pneumonia* and *pericarditis* recovered following steroid therapy. The recommendation of others [16] was followed in the successful treatment of a patient critically ill with *typhoid fever* by using ACTH and cortisone along with chloramphenicol.

TABLE 10

Patients with Drug Reactions and Treated with ACTH or Adrenocortical Steroids

No. Age-Sex	Causative Drug	Clinical Features	Treatment	Outcome
1. 1 M	Antitetanus horse serum	Severe serum sickness with fever and urticaria	Prednisone, 40 mg. daily × 5 30 mg. daily × 3	Recovered
2. 23 F	Penicillin	Fever, dermatitis, pharyngeal edema, splenomegaly	Cortisol, 100 mg. I.V. × 1 Cortisone (orally), 100 mg. daily × 4 50 mg. daily × 4 37.5 mg. daily × 1 25 mg. daily × 1 12.5 mg. daily × 1	Recovered
3. 24 F	Penicillin	Urticaria, pharyngeal edema	Cortisol, 100 mg. I.V. × 1 Cortisone, 75 mg. da. × 6	Recovered
4. 24 F	Penicillin	Critically ill with fever, chills, dermatitis, hepatomegaly, lymphadenopathy, hemoptysis, epistaxis, encephalopathy, convulsions	Cortisol, 100 mg. I.V. × 1 Cortisone, 100 mg. daily × 3 75 mg. daily × 1 50 mg. daily × 2 25 mg. daily × 2 15 mg. daily × 1 10 mg. daily × 1 ACTH, I.M., 40 mg. daily × 1 20 mg. daily × 4	Recovered
5. 27 M	Penicillin	Fever, chills, polyarthritis, urticaria	Cortisol, 200 mg. I.V. × 1 Prednisone, 30 mg. daily × 7 25 mg. daily × 3 20 mg. daily × 3 30 mg. daily × 9 ACTH, I.M., 40 mg. daily × 1 30 mg. daily × 1 60 mg. daily × 3 20 mg. daily × 1 10 mg. daily × 1	Recovered
6. 29 M	Penicillin	Fever, polyarthritis, urticaria	ACTH, I.M., 60 mg. daily × 2 10 mg. I.V. × 1 20 mg. I.V. × 1	Recovered
7. 35 F	Amidopyrine	Agranulocytosis, WBC 450, fever, severe pharyngeal edema	ACTH, I.M., 40 mg. daily × 1 40 mg. daily × 3 40 mg. daily × 2 40 mg. daily × 1 Cortisone, 30 mg. I.M. × 1	Recovered
8. 40 F	Tetracycline	Fever, dehydration, dermatitis, myalgia, arthralgia, diarrhea	Cortisone, 300 mg. orally × 1 200 mg. orally × 1 50 mg. orally × 1	Recovered
9. 46 M	Penicillin	Immediate reaction with impending collapse. Cyanosis followed by fever and urticaria	Cortisol, 100 mg. I.V. × 1	Recovered
10. 66 F	Codeine ASA comp.	Recurrent agranulocytosis, WBC 850 with 100% lymphocytes; no granulocytes for 15 days	Cortisol, 100 mg. b.i.d. × 2 Meticorten, 10 mg. t.i.d. × 2 5 mg. t.i.d. × 2	Recovered

Steroid Therapy for Drug Reactions

ACTH and the adrenocortical steroids have been highly effective in the management of selected patients with severe drug reactions. The observations in this clinic confirm the earlier studies of others.[17] A summary of 10 patients treated is given in table 10. Six of the 10 patients had hypersensitivity due to penicillin. All of the patients recovered. No undesirable effects resulted from the use of the steroids. Two patients (cases 7 and 10) suffered from severe agranulocytosis, and responded promptly to steroid therapy.

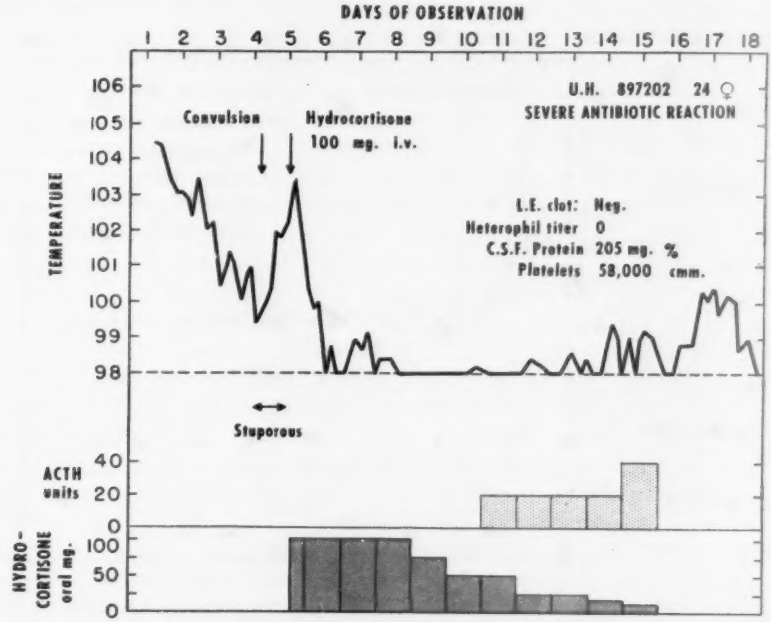


Fig. 21. Clinical course of 24 year old housewife critically ill as a result of penicillin hypersensitivity. She had encephalopathy with convulsions and coma. She responded promptly to cortisone. Although cortisone was given in decreasing doses and then ACTH was administered, subsequent experience indicates that the ACTH was not necessary.

One patient was critically ill with a severe penicillin reaction. Her course is presented in figure 21. She entered the hospital because of stupor and convulsions. Thrombopenia was present. The protein level in the cerebrospinal fluid was markedly elevated. Splenomegaly was detected. She responded favorably to hydrocortisone therapy. There were no residuals from this serious illness. She subsequently became pregnant and had a normal delivery. A second patient, the wife of a physician, was quite ill as a result of a penicillin reaction (figure 22). She also responded promptly to hydrocortisone and cortisone.

What Steroid? What Dose?

The studies on the patients included in this report have extended over a period of several years, which accounts largely for the variations in the therapeutic preparations and the doses of steroids used. The first group of patients received ACTH because this drug was readily available and effective. As more information became available and more potent compounds were introduced there has been a shift away from the use of ACTH and cortisone. Recently, hydrocortisone and some of its analogues have been used more frequently.

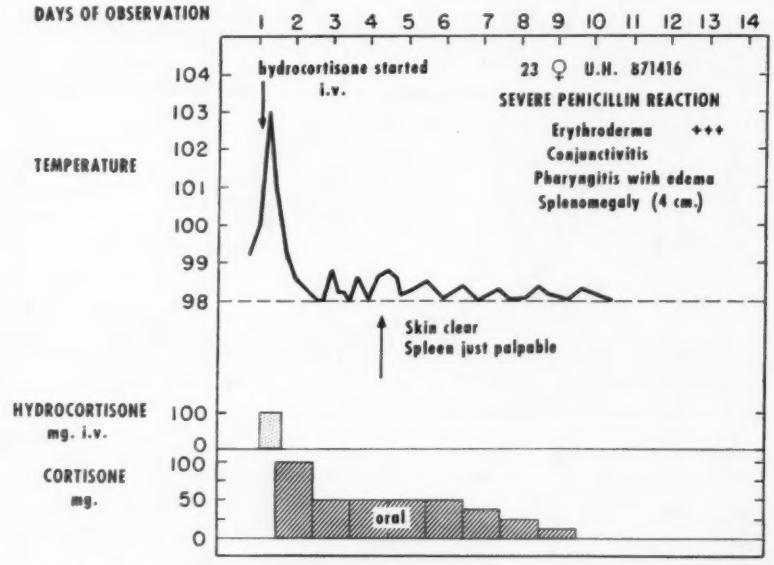


Fig. 22. Clinical course of 21 year old female who had a severe penicillin reaction. She responded favorably to hydrocortisone and to cortisone.

A survey of the conditions for which ACTH and the adrenal cortical steroids have been used shows that two general groups of illness were treated. Recognition of this differential has a direct bearing on the choice of steroid and dose to be employed. The first group includes those patients with infections, but the critical problem was that of peripheral vascular collapse. Observations on patients in this category, and studies in the laboratory on experimental shock, have clearly shown that the best results with steroid therapy follow the use of large doses of a parenterally administered steroid that is readily metabolized. For this reason, it is recommended that from 500 to 1,000 mg. of hydrocortisone be administered intravenously over a 24-hour period in two to three divided doses. Usually this intensive therapy

can be discontinued within four to five days. This therapeutic approach is shared by others, not only in the treatment of bacterial shock but in the management of hemorrhagic shock as well.[18, 19] At times, oral preparations can be employed after the initial intravenous administration of hydrocortisone. Oral therapy is sometimes indicated if treatment must be continued for several days. For this purpose, one of the analogues, such as prednisone, methylprednisolone or dexamethasone, can be used in equivalent doses. When large doses of steroids are given for only a few days, it is not necessary to reduce the dose gradually and to administer ACTH, as has been recommended when the adrenal cortical steroids are administered for long periods of time. No ill effects have been observed with the use of these large doses for a brief period of time. ACTH is not recommended either as the sole agent or as supplementary treatment during this intensive period of therapy.

The second large group of patients was suffering from the undesirable effects of inflammation, which were associated with infections or with drug hypersensitivity. In this group it is not so imperative that large parenteral doses of steroid be given. In fact, additional stimulation of the adrenal cortex with administered ACTH may be sufficient, though ACTH is now rarely used in this clinic for this purpose. For the critically ill patient, hydrocortisone is administered intravenously in a dose of 100 to 200 mg. every eight to 12 hours. Improvement is usually apparent after 24 to 48 hours, and then oral preparations of steroids can be employed in reduced amounts. These oral doses should be decreased as soon as the condition of the patient permits.

When intensive steroid therapy is carried out for an illness for which no specific chemotherapeutic agent is available, antibiotics are not usually employed prophylactically. Prophylactic antibiotic therapy is not recommended when steroid is used in the treatment of trichinosis. On the other hand, an antibiotic would be given to a patient receiving steroid who has had agranulocytosis induced by a drug.

Side-Effects of Steroids

An inventory of the patients treated in this study has revealed no significant ill effects when the steroids were administered for a period of only a few days, even when large doses were used. In fact, undesirable effects were noted in only two patients being treated with steroids for an infectious disease. It was necessary to administer steroids for several weeks to one patient with acute rheumatic fever and pancarditis. She had presented with a history of peptic ulcer. During the course of her treatment the ulcer became activated, a hemorrhage ensued, and a gastrectomy was carried out. She recovered. Another patient was presumed to have disseminated tuberculosis. His condition deteriorated with antituberculosis therapy, and steroids were administered almost as a last resort. He was proved to have

disseminated histoplasmosis, and it is not unlikely that further dissemination occurred as a result of steroid therapy. A third patient was being treated for a noninfectious condition, and a latent tuberculosis was activated. He had a discoid form of lupus erythematosus, and received hydrocortisone for this condition. He had a history of tuberculosis. He recovered after antituberculosis drugs were given. These constitute the only ill effects of steroids observed in a period of almost nine years.

Discussion

The introduction of ACTH and then of the adrenal cortical steroids as anti-inflammatory agents proved to be exciting for students of infectious diseases. This report has embraced the experience of one University Medical Center in the successful use of the steroids in selected patients. Although these drugs may provoke serious side-effects when administered for a long period of time, the intensive use of steroids for a brief period has not been associated with serious ill effects.

But the introduction of these compounds is of still greater significance from an over-all biologic point of view. The steroids have provided tools for the investigation of the dynamic phases of inflammation, which are so prominent in infections. In the host-parasite relationship it has permitted a partial separation of the desirable from the undesirable aspects of inflammation, as far as the host is concerned. The pathogenesis of acute peripheral vascular collapse is little understood. Investigations with the steroids have shown that these agents have immediate, and often marked, effects on the hemodynamics of circulation. Clinical observations and studies in experimental animals have revealed that large doses of selected adrenal cortical steroids can contribute to the reversibility of progressive deterioration in vascular collapse. Endotoxin shock and hemorrhagic shock have provided the models for further studies in this field.

The immediate objectives related to the use of steroids in infectious diseases should include a constant search for agents that will quickly subdue infections without provoking any serious side-effects. In the meantime, further clinical observations with the drugs now available are essential.

Summary

1. Adrenal cortical steroids and ACTH have been evaluated in 81 selected patients treated between 1950 and 1959 at the University of Minnesota Medical Center. This has included an analysis of two main groups of patients managed in this manner: first, patients with an infection and peripheral vascular collapse, and second, patients suffering from the ill effects of inflammation due to infections or to drugs.

2. Studies were made of 38 patients who had acute bacterial shock, 25 of whom had vascular collapse due to gram-negative endotoxin. Although

the mortality rate in the 38 patients was 60%, large doses of steroid did contribute to the recovery of certain patients. It is recommended that 500 to 1000 mg. of hydrocortisone be administered intravenously within the first 24 hours. Subsequent therapy with hydrocortisone or one of the analogues can often be confined to smaller doses given orally, and for a period of only a few days. The clinical observations have been substantiated by studies on experimental endotoxin shock in the laboratory.

3. Inflammation occurring during the course of an infectious disease can be highly deleterious when certain tissues are involved, such as those of the heart and central nervous system. Steroid therapy has been effective in selected cases of tuberculosis, brucellosis, infectious mononucleosis, the complications of mumps, which include orchitis, purpura and encephalomeningitis, acute rheumatic fever, hepatitis, trichinosis, and severe drug reactions, especially those due to penicillin.

4. The basic philosophy underlying the selective use of steroids in this medical center is the administration of large doses of adrenal cortical steroid to seriously ill patients for a brief period of time. No undesirable side-effects have been observed when these criteria have been followed. The benefits have far outweighed the possible hazards.

SUMMARIO IN INTERLINGUA

Steroides adrenocortical e ACTH esseva evalutate in 81 selecte patientes tractate inter 1950 e 1959 al Centro Medical del Universitate Minnesota. Esseva studiate 38 casos de acute choc bacterial, incluse 25 con collapso vascular causate per endotoxina gram-negative. Ben que le mortalitate in iste serie de 38 patientes esseva 60%, il es ver que massive doses de steroides contribueva al restablimento de certes del superviventes. Es recommendate que 500 a 1.000 mg de hydrocortisona es administrate per via intravenose in le curso del prime 24 horas. Le subsequente therapia con hydrocortisona o un de su analogos pote in multe casos esser restringite a plus basse doses que es alora administrate per via oral e solmente durante un periodo de alicun dies. Le observationes clinic esseva corroborate per studios laboratorial de choc endotoxinic experimental.

Un inflammation occurrente in le curso de un morbo infectiose pote esser multo nocive si certe typos de tissu es afficite, como per exemplo le tissus del corde e del systema nervose central. Therapia a steroides se ha monstrate multo efficace in selecte casos de tuberculose, brucellosis, mononucleosis infectiose, le complicationes de parotiditis (que include orchitis), purpura e encephalomeningitis, acute febre rheumatic, hepatitis, trichinosis, e sever reactiones drogal (specialmente illos causate per penicillina).

Le principios governante le selective uso de steroides a iste centro medical demanda le administration de grande doses de steroides adrenocortical durante breve periodos de tempore a patientes qui es seriemente malade. Nulle adverse effectos secundari esseva observate in tanto que iste criterios esseva mantenite. Le beneficios excedeva per multo le hasardos possibile.

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SHUNT ENCEPHALOMYELOPATHY. I. RECURRENT PROTEIN ENCEPHALOPATHY WITH RESPONSE TO ARGININE *

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The neuropsychiatric complications of spontaneous or surgically induced portal-systemic shunts have been widely observed and extensively discussed, so the most frequent clinical patterns are now common knowledge. Various more obscure and infrequent but no less fascinating manifestations of these complications are becoming evident as our awareness of the clinical entity increases. Two such manifestations have been observed in patients described in this report. The first is the occurrence of extreme and progressive protein intolerance, with correction of the recurrent toxic states by large doses of arginine. The second, elaborated upon in the companion paper that follows, is the occurrence of permanent neuropathologic changes in the spinal cord.

Case Reports

Case 1. An intelligent 53 year old tool-and-die maker was transferred to this hospital because of recurrent episodes of protein coma and spastic paraplegia. He gave no history of alcoholism.

Twenty years before admission here he had experienced the first of several hematemeses, for which a gastroenterostomy had been performed. Five, 10 and 11 years later he had had recurrent severe episodes of upper gastrointestinal bleeding, for which he was treated symptomatically. After another severe recurrence in three years, a Billroth II gastrectomy was performed, at which time an enlarged liver and spleen were seen, and a liver biopsy showed portal cirrhosis. Three years following the gastrectomy he had two recurrences of hematemesis, and an effective portacaval shunt was performed. An old thrombus was seen in the portal vein, and liver biopsy again showed cirrhosis. This was 17 years after the first episode of bleeding. Within two weeks of surgery he began to have periods of disorientation and unconsciousness, which recurred intermittently. When seen by a neurologist six weeks after the shunt he was confused, disoriented and lethargic. These manifestations were more or less continuous, though accentuated in the late afternoon and evening. His speech was jargon. A staggering gait, ataxia and nystagmus were prominent. The reflexes were normal. He was thought to have a toxic encephalopathy and psychosis. Improvement was said to follow when barbiturate sedation was withdrawn and protein hydrolysates were substituted for protein in the diet.

Eighteen months after the shunt procedure the patient entered a veterans hospital in transfer from a domiciliary home. He had had recurrent episodes of

* Received for publication October 14, 1959.

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tremulousness, somnolence and unsteadiness. After hospitalization he had three episodes of psychotic behavior and tremulousness, precipitated by high protein diets. With the last he was comatose for one day. Recovery followed protein restriction, and he was maintained thereafter on 20 to 35 gm. of protein. However, he still had recurrent mild episodes of tremulousness, confusion and aberrant behavior. Hematologic studies revealed a hemolytic anemia, with reticulocytosis, elevated fecal urobilinogen excretion, and a normoblastic marrow. Five months after admission he first noticed an unbalanced feeling when standing or walking. This was the beginning of progressive paresis and, ultimately, spastic paralysis, which developed over the next nine months before he was transferred to our hospital. For six months before transfer to this hospital he received weekly intramuscular injections of 6 ml. crude liver extract.

TABLE 1

Abbreviations and Units of Measurement of Various Laboratory Tests

A/G—serum alb./glob., gm.%
AP—alkaline p'tase, KA units
BM—bone marrow
BS—blood sugar, mg.%
BSP—bromsulfalein in 45', %
BSP_c—corrected BSP, %
BUN—blood urea nitrogen, mg.%
Ca—serum calcium, mg.%
Cbs—Coombs' test
Cl—serum chloride, mEq./L.
CF—Ceph. flocc., 48 hr.
CO_2—CO_2 comb. power, mEq./L.
FBS—fasting blood sugar, mg.%
FF—fecal fat, gm./d.
FN—fecal nitrogen, gm./d.
FU—fecal urobilinogen, mg./d.
Hb—hemoglobin, gm.%
Ht—hematocrit, %
K—serum potassium, mEq./L.
MCC—mean corp. hb. conc., %
MCV—mean corp. vol., μ^3
Mg—serum magnesium, mEq./L.
Na—serum sodium, mEq./L.
NH_3—blood ammonia, μg.%
1'/TB—1'/tot. ser. bilirubin, mg.%
P—serum phosphorus, mg.%
PA—blood pyruvic acid, mg.%
PC—prothrombin conc., %
Plt—platelets, thousands/mm.^{3}
RTC—reticulocytes, %
SR—sedimentation rate, mm./hr.
StG—stool guaiac
TC—tot. ser. cholesterol, mg.%
TT—thymol turbidity, units
UAA—urine amino acid, gm./d.
UN—urine nitrogen, gm./d.
UU—urine urobilinogen, mg./d.
Wbc—white count, c./mm.^{3}/10^3

The patient was alert on admission here. His liver was not palpable; however, splenomegaly, ascites and edema were prominent, as was the spastic paraplegia. His hepatic abnormality was unchanged, and his hemolytic anemia persisted. Cranial nerves, cerebellar functions, and deep and superficial sensation were all normal. The initial and subsequent laboratory studies of importance are given in table 2. Table 1 lists the abbreviations and units of measurement of the various laboratory tests. In addition, spinal fluid studies during the first and fourth weeks and a myelogram were normal.

The essentials of the patient's course over a 59-week period of hospitalization are listed in table 2. Initially he received 20, then 30 gm. of protein in his diet, with large supplemental doses of parenteral B complex vitamins including massive doses of vitamin B_{12}. Though having marked spasticity and nearly complete paralysis of his legs, he was able to waggle his toes and move his feet minimally, and to stand with support. Since he seemed to tolerate 30 gm. of protein well for more than two weeks, an attempt was made to increase his protein intake, with disastrous results as soon as 50 gm. per day were exceeded. On the first day of the fifth week, having exceeded 50 gm. for two days, he lapsed rather rapidly into deep coma, which responded within 24 hours to 75 gm. of arginine hydrochloride intravenously. The sequence of changes in mental state and blood ammonia, pyruvic acid and urea nitrogen during this episode is given in table 3.

Following this brief period of coma the paralysis of the patient's legs and feet was complete. There was never any subsequent voluntary movement, and he was

TABLE 2—Sequential Hospital Course of Case 1 in Relation to Therapy

Week	Body Wt.	Mental and Motor State	Protein, grams	Amino Acid, grams	Antibiotics, grams/d.	Transfusions, ml.	Relevant Laboratory Tests
1	172	Minimal movement legs, sensorium clear	20–30	—	—	—	Hb 10.8, Wbc 2.9, MCV 94, MCC 34, A/G 1.9/2.4, 1′/TB 0.6/1.9, BSP 36, CF 3+, TT 3.2, PC 43, TC 108, UU 1.0, BUN 9, Na 148, K 4.2, Mg 1.40, CO_2 23, Cl 120, Ca 8.8, P 3.4
2–4	173	Sensorium clear	30–60	—	—	—	Hb 10.6, Wbc 3.1, RTC 2.9, Plt 29, AP 18, UCP 385, FF 37, FN 3.7, FU 456, BM: 29% normoblasts
5	173	Coma 24 hrs., alert next evening, ate supper	70 1 d. then 20	AH 75 IV AH 25 Or/d.	—	—	Hb 11.2, 1′/TB 0.7/3.2, BUN 16, CO_2 19, Cl 127
6	173	Slight confusion, weak grasp	20	AH 25 Or/d.	—	—	Hb 10.7, RTC 2.5, Plt 81, StG —, BUN 15, CO_2 21, Cl 113
7	—	Sensorium clear	45	AH 12.5 Or/d.	—	—	Hb 9.9, BUN 12, UU 0.3
8–9	—	Up in wheel-chair	50	AH 25 Or/d.	—	B 500	Hb 10.5, A/G 1.4/2.7, NH_3 235, PA 1.37, CO_2 24, Cl 114
10	—	Wh-ch., S. clear	45	AH 25 Or/d.	—	—	Hb 9.4, Wbc 1.9, SR 10, NH_3 217, PA 2.25, CO_2 28, Cl 118
11–12	177	Wh-ch., S. clear	50	AH 25 Or/d.	—	—	Hb 10.1, NH_3 205, PA 1.10, StG —, Na 148, K 4.3
13–14	188	Wh-ch., lethargic 1 d.	55	AH 25 Or/d.	—	—	Hb 10.9, A/G 1.8/2.9, NH_3 232, PA 1.75
15–16	187	Wh-ch., drowsy, lethargic 1 d.	55	AH 25 Or/d. d.c.	—	—	Hb 11.1, NH_3 162, PA 1.28, FN 3.4, Na 143, K 4.1
17	175	Headache, shaky 2 d.	45	—	—	B 500	Hb 11.3, A/G 1.7/2.5, FN 2.5, FF 16, UN 6.6, UAA 0.10
18	176	Tremulous, lethargic, incontinent	45	AH 100 IV	—	B 500	Hb 13.0, A/G 1.8/2.7, NH_3 276, PA 1.30, CO_2 23, Cl 112
19–20	175	Wh-ch., S. clear	45	—	—	—	Hb 12.5, Na 143, K 4.5, CO_2 26, Cl 110
21	170	Confused, tremulous, then clear	35	AG 100 IV	—	—	Hb 12.0, Na 140, K 4.6, CO_2 26, Cl 116
22	—	Drowsy, confused after Trypto., clear next d.	35	Trypto 2 IV	—	—	Hb 12.7, A/G 2.1/2.8, Mg 1.54
23	171	Confused, coma, awake next d., confused and incoherent rest of week	30	AH 100 IV	Neo 4.0	—	Hb 12.0, BUN 8, Na 142, K 4.6, CO_2 27, Cl 112
24	169	Sensorium clear, fecal incontinence	25	—	Neo 4.0	—	Hb 10.4, A/G 1.7/2.4, Na 138, K 4.2, Mg 1.64, CO_2 25, Cl 111
25–29	165	Wh-ch., S. clear	25	—	Neo 4.0 d.c.	—	Hb 11.0, Wbc 6.9, SR 17, RTC 1.8, Plt 39, NH_3 273, PA 2.12
30	162	Drowsy, lethargic 1 d. afte st transfusion	25	—	—	P 1500	A/G 1.6/2.8, 1′/TB 0.8/2.2, BUN 7, K 3.9, CO_2 26, Cl 118
31	160	Wh-ch., S. clear	25	—	—	P 1000	NH_3 250, PA 1.70, BUN 6
32	159	Wh-ch., S. clear	25	—	Chloro 1.5 +Neo 8.0	P 2000	A/G 1.7/2.7
33–34	160	Wh-ch., S. clear	30	—	Neo 4.0	—	A/G 1.7/2.9
35	160	Wh-ch., S. clear	25	—	Neo 4.0 d.c.	B 1000	Hb 8.6 & 8.7, Wbc 1.8, SR 10, Plt 14 & 25, RTC 1.0, 1′/TB 1.5/4.9, FU 15, 2 StG –
36	155	Confused, disoriented, lethargic, incontinent 1 d.	25	—	—	P 250	Hb 12.0, Wbc 5.2, SR 15, BSP_e 30, AP 14, CF 4+, TT 1.9
37	152	Wh-ch., S. clear	25	—	Neo 4.0	—	Hb 11.0
38	151	Wh-ch., S. clear	25	AH 25 IV	Neo 4.0	P 1250	A/G 1.5/3.0, UU 3.8
39	150	Listless, incontinent, semi-coma 1 d. after P., S. clear, rational 1 d. after AH	25	AH 50 IV	Neo 4.0	P 1500	A/G 1.8/2.9, BUN 11, Na 144, K 4.2, Cl 119
40	148	Somnolent, Wh-ch., S. clear after AH	25	AH 50 IV	Neo 4.0	—	A/G 1.5/3.2, Mg 1.30
41	152	Confused, lethargic, incontinent last 2 d.	25	AH 25 IV	Neo 4.0 d.c.	—	Hb 8.4, Wbc 4.2, Plt 20
42	150	Episode of semi-coma	25	AH 50 IV	—	C 250	Hb 7.8, Wbc 5.6, SR 32, K 4.2, Mg 1.30
43–44	150	Alert	25	—	Chloro 1.5	C 500	Hb 9.5, Plt 20, A/G 1.4/3.2, 1′/TB 3.1/5.4, UN 6.3, UAA 0.07
45–49	146	Mostly alert, brief "spells"	25	—	—	—	Hb 8.2–9.5, A/G 1.6/2.7, Mg 1.42, UN 5.8, UAA 0.08
50	145	Mostly alert, Wh-ch.	25	—	—	C 500	Hb 10.1, UN 5.4, UAA 0.08
51	147	Irrational, incontinent, semi-coma	25	AH 100 IV	—	—	Hb 10.7
52–53	146	Recovery, episodes confusion, trances	25	—	—	—	Mg 1.40
54	143	Deep coma, recovery, relapse, lethargy, the n alert	25	AG 100 IV AG 100 IV	—	—	Hb 8.0
55–57	137	Episodes somnolence, alert at times	25	—	—	—	BUN 23, NA 131, K 4.1, Mg 1.42
58	135	Coma, incontinent, recovery, up in Wh-ch.	25	AG 50 IV	—	—	
59	133	Incoherent, lethargic, response to AG Relapse, coma, death	—	AG 250 IV AG 200 IV	—	—	Hb 8.4, K 5.1

Abbreviations (except lab. tests): AH, Arginine hydrochloride. AG, Arginine glutamate. IV, intravenously. Or, orally. Wh-ch., up in wheel-chair. S., sensorium. B, whole blood. P, plasma. C, packed red cells. d.c., discontinued. Trypto, Tryptophane. Neo, Neomycin. Chloro, Chloromycetin. Tetra, Tetracycline. Erythro, Erythromycin. Alba, Albamycin.

unable to stand up. During the following 12 months he had many episodes of precoma or coma. Characteristically, these were preceded by a variable period (up to one or two days) of irritability, belligerence, slurring speech, increased salivation, disorientation, confusion, blurred vision, crying, picking, incoördination, mechanical movements, tremor, psychotic behavior, and urinary and fecal incontinence. Then would follow grimacing, grasping, flapping tremor, somnolence, lethargy and ultimately, stupor and coma.

From the seventh to the twentieth week the patient received 45 to 55 gm. of protein per day, which he tolerated reasonably well, though he had recurrent episodes of precoma. Thereafter this had to be reduced to 25 gm. Attempts were made at different times to increase his protein tolerance by the use of oral arginine and oral neomycin. The oral arginine was given in rather small dosage and, in retrospect,

TABLE 3

Sequence of Mental and Chemical Changes in Case 1 during Episode of Protein Coma Treated with Arginine Hydrochloride

Days since Adm.	Time	Mental State and Treatment	Blood NH_3-N, μg.%	Pyruvic Acid, mg.%	BUN, mg.%
23	8:00 a.m.	Alert	209	1.84	11.5
29	1:00 p.m.	Headache, alert			
	10:30 p.m.	Fell out of bed, confused, restless, picking			
30	1:00 a.m.	Responding poorly			
	2:00 a.m.	Unconscious, flushed, perspiring, frothing Deep stertorous breathing, last rites by priest			
	3:00 a.m.	Arginine HCl 25 gm. IV over 4 hrs., deeply comatose			
	8:00 a.m.	Arginine HCl 25 gm. IV over 4 hrs.			
	8:30 a.m.	Comatose, no response	439	4.43	14.0
	11:45 a.m.	Comatose but appears to hear			
	12:00 n.	Arginine HCl 25 gm. IV over 7 hrs.			
	2:30 p.m.	Coma but response to pain	225	2.75	—
	5:00 p.m.	Quiet breathing, no response to light stimuli			
	10:00 p.m.	Responds to light stimuli			
31	6:00 a.m.	Responds when name called			
	8:00 a.m.	Answers when spoken to, drowsy	187	1.94	15.5
	10:00 a.m.	Awake, memory hazy			
	5:00 p.m.	Alert, ate supper alone			
32	6:00 a.m.	Alert, well oriented and conversive			
33	8:00 a.m.	Alert	209	1.54	13.0
36	8:00 a.m.	Alert	190	1.39	14.0
47	8:00 a.m.	Alert	152	1.42	12.0
Normal limits			150	1.50	20.0

may have been of some benefit, though at the time it was considered to be ineffective. The neomycin was given three different times, and may also have been of some benefit, though it did not prevent the occurrence of episodes. Several precoma episodes seemed directly correlated with blood or plasma transfusions; however, this could have been coincidental (though we think not). On one occasion, 2 gm. of tryptophan given intravenously precipitated drowsiness and confusion, which cleared spontaneously.

Twelve electroencephalograms were taken during the period from the eighth to the twenty-second week. None was entirely normal. The most nearly normal electroencephalogram is shown in figure 1A, taken during the seventeenth week. Similar electroencephalograms were recorded during the eighth, tenth, eighteenth, nineteenth and twenty-first weeks. Samples of the most abnormal tracings recorded are shown in figures 1B and 1C. These were observed during an episode of precoma occurring on the fourth day of the eighteenth week. Two days later, following 100 gm. of arginine hydrochloride intravenously, a tracing very similar to figure 1A was obtained. On three other occasions a deterioration of the electroencephalogram,

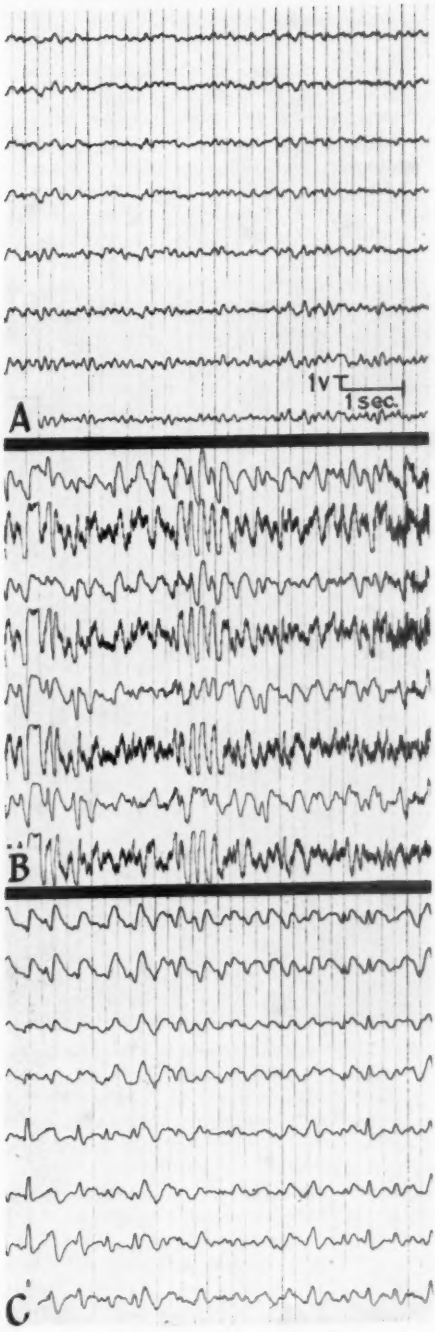


FIG. 1. Electroencephalograms of case 1 recorded during the seventeenth (A) and eighteenth (B and C) weeks. In each electroencephalogram the paired leads are, from top to bottom, the left and right frontal, central, parietal, and occipital leads.

intermediate between those seen in figure 1A and figures 1B and 1C, was documented. The first occurred during the sixteenth week, on a day when the patient was drowsy, lethargic and difficult to arouse. Two days later the tracing of figure 1A was recorded. The second occurred on the first day of the twenty-first week, when similar symptoms were observed. Both symptoms and electroencephalographic changes responded to intravenous arginine. The last recorded deterioration of the electroencephalogram was observed during the twenty-second week, directly following an experimental infusion of 2 gm. of tryptophan intravenously, when transient confusion and somnolence occurred.

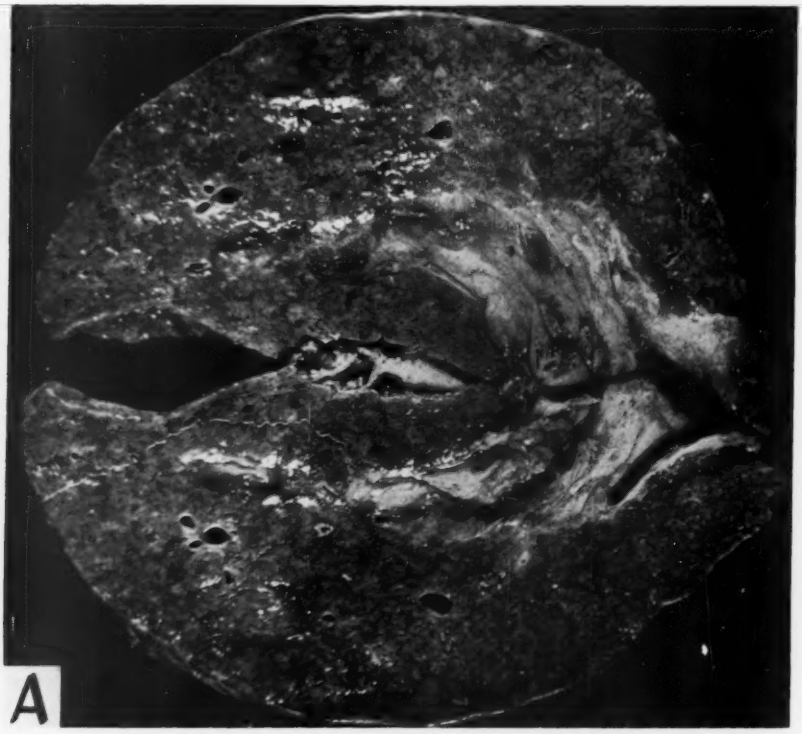


FIG. 2A. Gross section of liver of case 1 at necropsy.

Hypoalbuminemia, edema and ascites were never controlled, despite repeated plasma transfusions. Hyperchloremia, which seemed to be correlated with reductions in serum proteins and bicarbonate, was persistent throughout. The patient's course was steadily downhill with wasting of body protein stores. Total nitrogen and amino acid excretion decreased correspondingly. From the forty-fourth to the fiftieth week, 37 24-hour urine collections were analyzed for total and amino acid nitrogen. The averaged values for the intervals listed are given in table 2. Amino acid excretion was less than one fifth of normal, and total nitrogen excretion was about two fifths of normal.

Protein sensitivity seemed to be progressive. Aside from the countless episodes

of somnolence and aberrant behavior, the patient had 13 episodes treated with arginine hydrochloride or arginine glutamate intravenously, with good response in all but the last. Typically, 50 to 100 gm. were required and were given in 10% glucose in water over a period of from four to eight hours. In one year he received a total of 1,375 gm. of arginine or arginine glutamate intravenously. The amino acid seemed to be specific for his episodes. The last episode followed an unrecognized perforation of a stomal ulcer. The patient died following four days of coma which responded transiently to arginine intravenously.

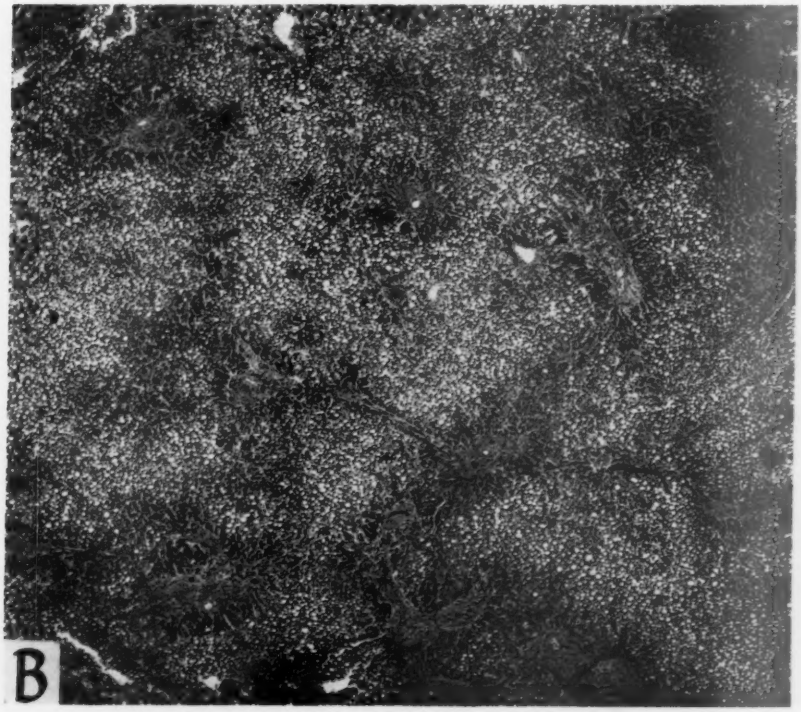


FIG. 2B. Microscopic section of liver of case 1 at necropsy.

Autopsy: At gross autopsy examination an emaciated, icteric individual, 74 inches in length and weighing 133 pounds, was described. Two liters of cloudy yellow fluid were found in the abdominal cavity, from which were cultured *Escherichia coli,* alpha streptococci and hemolytic staphylococci. One liter of clear yellow fluid was present in the right hemithorax, and 200 ml. were present in the left. The heart weighed 380 gm.; right lung, 880 gm.; left lung, 630 gm. The liver weighed 950 gm. and was finely but markedly nodular (figure 2). The spleen weighed 560 gm. The pancreas weighed 120 gm. and was extensively fibrotic. The adrenals and kidneys appeared to be normal. An extensive Billroth II gastric resection (approximately 90%) was evident, the stomach remnant weighing 42 gm. A 4 by 2 cm. leiomyoma was seen in the proximal loop of the small bowel, and a 1.5 cm. penetrating ulcer with a small, 1 to 2 mm. perforation was found in the efferent loop, about

4 cm. from the gastroenterostomy. Esophageal varices were present showing evidence of recent bleeding, and the remainder of the gastrointestinal tract contained small amounts of dark blood. The portacaval anastomosis was widely patent. About 3 cm. and 7 cm. from the orifice, calcified plaques were found in the portal vein. The latter was patent throughout.

Microscopically, brown atrophy was seen in the heart, and the lungs were normal. In the liver, fatty metamorphosis and cirrhosis were evident, and iron was present in large amounts (figure 2). Fibrosis was prominent in the spleen. Marked fibrosis was evident in the pancreas, which also contained much iron. The kidneys

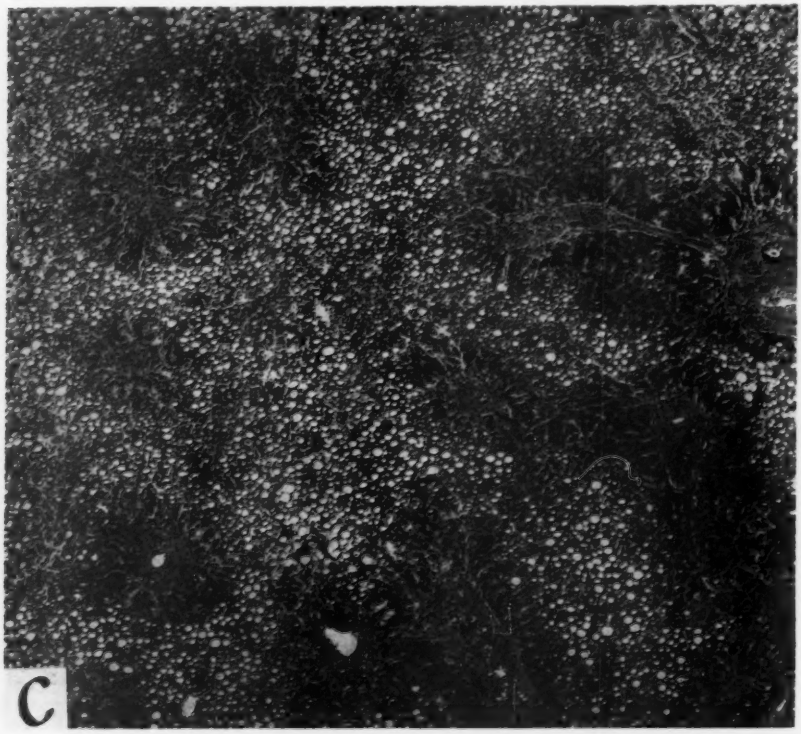


FIG. 2C. Magnification of microscopic section of liver of case 1 at necropsy.

showed thickening and hyalinization of the glomerular basement membranes. Esophagitis was marked, and dilated submucosal veins were prominent. The jejunal ulcer was active and penetrated deeply. Spongy degeneration of the putamen and pyramidal tract demyelination in the spinal cord were the essential neuropathologic findings. (Details of neuropathologic findings are included in "Shunt Encephalomyelopathy. II," in this issue.)

Final Diagnoses: Acute stomal ulcer with perforation and generalized peritonitis as the immediate cause of death, fatty metamorphosis, portal cirrhosis, hemosiderosis of liver and pancreas, pancreatic fibrosis, hyalinization of glomerular basement membranes of kidneys, postoperative portacaval shunt and Billroth II gastric resection,

esophagitis and esophageal varices, encephalomyelopathy and pyramidal tract demyelination.

Case 2. A 38 year old white male was admitted complaining of paralysis of his legs of one week's duration. He had first noticed difficulty in maintaining his balance three months earlier. This was followed in a month by weakness of the legs, and had progressed to complete paralysis and urinary and fecal incontinence by the time of admission.

He had been a severe chronic alcoholic for 12 years, and had had nine previous admissions to this hospital. The first admission, six years earlier, had been for

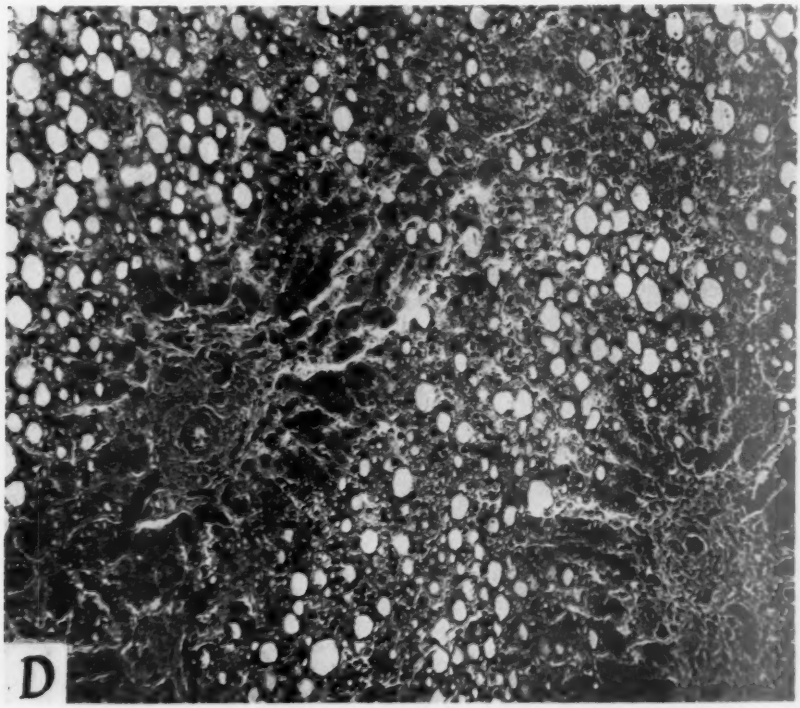


FIG. 2D. Further magnification of microscopic section of liver of case 1 at necropsy.

hematemesis. A duodenal ulcer was demonstrated by x-ray, and a liver biopsy showed portal cirrhosis. No varices were seen. Six months later hemorrhoidectomy was performed. One year after the first hospitalization for peptic ulcer the patient was re-admitted with severe malnutrition and massive ascites and edema. The signs of deficiency disappeared, but there was little improvement in the ascites by the time of discharge. He was re-admitted three months later because of marked ascites and edema. At this time his serum albumin was normal. After an unsuccessful trial of medical management over a period of four months, a portacaval shunt was performed for the intractable ascites, with good results.

The patient's fifth admission, this time for hematemesis and melena, followed the shunt procedure by six months. A gastrointestinal x-ray series showed an active

TABLE 4

Sequential Hospital Course of Case 2 in Relation to Therapy

Week	Body Wt.	Mental and Motor State	Protein, grams	Amino Acid, grams	Antibiotics, grams/d.	Relevant Laboratory Tests
1–2	188	Sensorium clear, spastic paraplegia Tremor, incontinent, up in wheel-chair	40	—	—	Hb 11.2, Wbc 5.6, RTC 5.1, Plt 84, SR 38, A/G 1.5/4.4 1′/TB 1.5/4.4, BSP, 41, CF 4+, TT 6, AP 24, StG —, Na 141, K 3.4, Mg 1.52, CO_2 24, Cl 115, Ca 8.2, P 3.8
3	—	Deep coma 1 d., response to arginine	40	AH 150 IV	Tetra 2.0	Hb 11.7, Ht 35, PC 27, 1′/TB 1.1/2.9, TC 97, Na 138, K 2.9, Mg 1.56, CO_2 19, Cl 118, Ca 7.0, P 3.0, A/G 1.2/3.9
4	186	S. clear, paranoid, irritable, tingling hands and feet	40	—	Tetra 2.0	1′/TB 1.2/2.6, BSP_5 44, PC 26, 2 StG —, Na 142, K 3.3, CO_2 21, Cl 115, Ca 7.9, P 3.7
5	188	S. clear, anxious, depressed, tremor (flap) 1 d.	40	—	Tetra 2.0	1′/TB 1.4/3.0, A/G 1.3/3.8, BUN 7, Na 144, K 3.2, CO_2 29, Cl 104
6	192	S. clear, anxious, diarrhea, stands with support	40	—	Tetra 2.0	Mg 1.48
7-8	193	S. clear, diarrhea	80	—	Tetra 2.0 d.c.	—
9	200	Confused, disoriented, slurred speech, lethargic, incoherent, tremor, all 4 d., then recovery	40	—	Neo 1.0×3	Na 144, K 3.3, Mg 1.56, CO_2 22, Cl 117, Ca 8.0
10	—	Confused, depressed, irritable, lethargic, tremor, all 1 d., then up in Wh-ch.	40	AH 50 IV	Tetra 1.0	BUN 10, FBS 124, Na 146, K 3.4, CO_2 17, Cl 122
11	189	Unconsc. 1 d., recovery, then confused	40	AH 25 IV	Neo 2.0	Hb 8.3, Ht 29, Wbc 5.1, MCV 100, MCC 30, FBS 124, Mg 2.12, CO_2 22, Cl 117
12	185	Lethargy, coma 1 d., stuporous, drowsy, abscess buttocks	40	AH 50 IV	Chloro 2.0+ Erythro 2.0	Hb 8.0, Wbc 9.4, 3 StG —, Cbs —, A/G 1.2/4.3, BUN 10 1′/TB 1.8/3.6, BSP_5 28, AP 12, Na 136, K 3.2, CO_2 18, Cl 118, Ca 7.5, P 3.2
13	178	S. clear, abscess drained	40	—	Chloro 2.0+ Erythro 2.0 d.c.	NH_3 211, BUN 10, FBS 90
14	170	Tremor, confused, lethargic, all 3 d.	20	AH 125 IV	Alba 1.0	Na 136, K 3.2
15	167	Tremor marked, drowsy, lethargy, coma 1 d.	20	AH 50 IV	Alba 1.0	Hb 5.2, Ht 17, RTC 1.2, Plt 19, PC 23, 1′/TB 0.8/2.2
16	175	S. clear, Wh-ch.	20	—	Alba 1.0	Hb 5.7, Trsfn B 300
17	179	Xmas pass, ret. in 1 d., confused, very lethargic, tremor, clear 1 d., then coma 1 d.	20 in hosp.	AH 50 IV	Alba 1.0	Na 143, K 3.5, Mg 1.94, CO_2 18, Cl 115
18	175	S. clear, Wh-ch.	20	—	Alba 1.0+ Neo 1.5+ Chloro 2.0	Hb 7.3
19	178	S. clear, Wh-ch.	20	—	Chloro+Neo	—
20	—	S. clear, Wh-ch.	20	—	Chloro	—
21	—	Confused, restless, tremor, lethargic	20	—	None	BUN 6, Na 143, K 3.2, CO_2 22, Cl 111
22	178	S. clear, Wh-ch.	20	—	None	A/G 1.1/3.9, 1′/TB 1.4/3.2, TC 97
23	178	Confused, restless, messy, tremor (flap)	20	—	None	PC 12, AP 27, TT 6, CF 4+
24	180	Restless, belligerent, alert, then listless, lethargic, confused, coma 2 d., death	20	AH 50 IV+ AG 100 IV	None	—

For abbreviations see tables 1 and 2.

duodenal ulcer and no varices. There was no edema or ascites. However, peripheral neuritis was evident, with numbness and tingling of hands and feet, depressed reflexes, and neurogenic bladder with retention. These responded to ordinary diet and care, after which the patient was discharged. Eight months later he returned for the sixth time, with massive hematemesis requiring 30 units of blood. Again an active duodenal ulcer was demonstrated on x-ray, and no varices were seen. The patient was treated conservatively, with healing of the ulcer.

The seventh admission, again for a bleeding duodenal ulcer, followed the shunt procedure by two years. A segmental gastric resection was carried out two months later. The portal pressure was rechecked, and was 19 cm. of water. At the time of surgery bromsulfalein retention was 25%; serum bilirubin, 1.9 mg.%; cephalin flocculation, 1 plus in 48 hours; thymol turbidity, 8 units; albumin-globulin ratio, 3.9/2.8. Recovery was uneventful.

TABLE 5

Sequence of Mental Changes in Case 2 during His First Episode of Coma

Days Since Adm.	Time	Mental State and Treatment
15	7:45 a.m.	Alert, Chloral hydrate, 0.3 gm.
	8:30 a.m.	Myelogram
	4:00 p.m.	Responds reluctantly
	5:00 p.m.	Ate supper, had to be fed
	9:00 p.m.	Sleeping all evening, poor response to stimuli
	10:30 p.m.	Groaning, coughing
	12:00 Midnight	Unconscious, annointed by priest Arginine HCl, 50 gm. IV over 4 hrs.
16	3:00 a.m.	Comatose
	5:00 a.m.	Coughing, no response to pain
	6:00 a.m.	Breathing more easily, moaning
	8:30 a.m.	Unresponsive but moaning
	12:30 p.m.	Resists suctioning
	3:00 p.m.	Arginine HCl, 50 gm. IV over 5 hrs.
	4:00 p.m.	Responds to pain somewhat
	6:00 p.m.	Still poor response to stimuli
	8:00 p.m.	Arginine HCl, 50 gm. IV over 4 hrs.
	12:00 Midnight	Responding to stimuli, much coughing
17	4:00 a.m.	Responds to questions
	6:00 a.m.	Asking for water, complains of pain
	10:00 a.m.	Responding well, great thirst
	6:00 p.m.	Ate supper, asking to see family

Six months after the gastric resection the patient returned for the eighth time, with jaundice, malnutrition and melena. His ascites had recurred, and he had lost 40 pounds since the gastrectomy. There was no evidence of recurrent peptic ulcer or varices on x-ray, and he was believed to have an alcoholic gastritis. At this time bromsulfalein retention was 28%; serum bilirubin, 8.0 mg.%; cephalin flocculation, 4 plus in 48 hours; thymol turbidity, 8 units; cholesterol, 141 mg.%; albumin-globulin ratio, 1.9/3.3. Improvement was very slow. At one time the patient was very somnolent and lethargic, and so was given 50 gm. of sodium glutamate and 50 gm. of potassium glutamate intravenously, with some improvement in his mental state. By the end of three and one-half months he had improved sufficiently to be discharged. At this time his albumin-globulin ratio was 2.3/3.5. He responded to mercurial diuretics, though re-accumulating fluid persistently.

The patient was not seen again for one year, when he was admitted intoxicated and complaining of fresh blood in his stools. There was no evidence of gastrointestinal bleeding. His hepatic function was poor, as before. His bizarre behavior led to a neuropsychiatric evaluation by court order, and he was committed to a state

hospital. At this time he showed evidence of organic brain damage, though he had no focal neurologic findings.

The present (tenth) admission occurred nine months later. On physical examination the patient was poorly nourished, belligerent and lethargic. Jaundice, edema and ascites were prominent, as was the spastic paraplegia. There were numerous spider nevi. The liver was enlarged and the testes were atrophic. The patient was unable to sit up, and was incontinent of urine and feces. The pertinent serial laboratory findings are given in table 4. In addition to these data, serologic tests for syphilis were negative, the spinal fluid pressure was normal, and spinal fluid protein was 115 mg.%. A spinogram and a cerebral angiogram were normal.

The patient's hospital course is outlined sequentially in relation to therapy in table 4. He was initially given a 40-gm. protein diet, with large supplements of B complex vitamins. His spastic paraplegia and urinary and fecal incontinence persisted until death. During the third week of hospitalization he had the first (table 5) of nine episodes of coma or precoma, which were in many respects similar to those observed in case 1. Characteristically, these episodes were preceded by a variable period (several hours up to one or two days) of irritability, tremor of hands with incoördination, increased salivation, slurred speech, crying spells, repetitious talking, grimacing, blinking, irrationality, confusion, disorientation, somnolence, lethargy, sometimes flapping of arms and, finally, stupor and coma.

The episodes of precoma or coma appeared to be more or less related to dietary protein intake, and the patient was ultimately limited to 20 gm. of protein per day. Protein sensitivity seemed to be progressive as his nutritional state deteriorated. Intravenous arginine, as in the first case, seemed to be specific therapy for his precoma or coma episodes, though there were a few other occasions short of coma where improvement was spontaneous. Arginine was given as the hydrochloride or glutamate, 50 gm. in 1 L. of 10% glucose in water, infused slowly over a period of from four to eight hours, and repeated if necessary. Characteristically, the patient began to respond before the end of the infusion, and his sensorium would clear by the next day. A total of 650 gm. of arginine was given intravenously during his five-month period of hospitalization.

Broad-spectrum antibiotics were given continuously from the third to the twentieth week, without remarkable effects on the episodes of precoma or coma, with the possible exception of the eighteenth to twentieth week, when the sensorium remained clear.

The patient's course was one of progressive deterioration. Ascites and edema were never controlled, and hypoalbuminemia was severe and persistent. Like case 1, he also had a persistent hyperchloremia. He had no further bleeding, but his hemoglobin concentration dropped from 11.2 gm.% to 5.2 gm.%, probably because of multiple factors, among which we considered protein insufficiency, hemodilution, toxicity of broad-spectrum antibiotics, and apparent hemolysis. There was general wasting as protein stores were lost. The patient died five months and one week after admission, following a three-day episode of coma which did not respond to arginine. All efforts to secure an autopsy failed. Liver biopsies obtained during the first, fourth and seventh admissions are shown in figure 3.

Case 3. A 49 year old white man was first seen in this hospital 18½ months before his death. One year previously he had first noticed midabdominal pain and a sensation of distention following meals. Three months later he had an episode of severe abdominal pain with vomiting, for which he was hospitalized. An x-ray was said to show a peptic ulcer, for which he was treated, with gradual improvement. However, after six months he began to have five or six large soft bowel movements daily, with associated periumbilical cramping. He lost 44 pounds, though his appetite was good. On examination here he was not undernourished, although showing

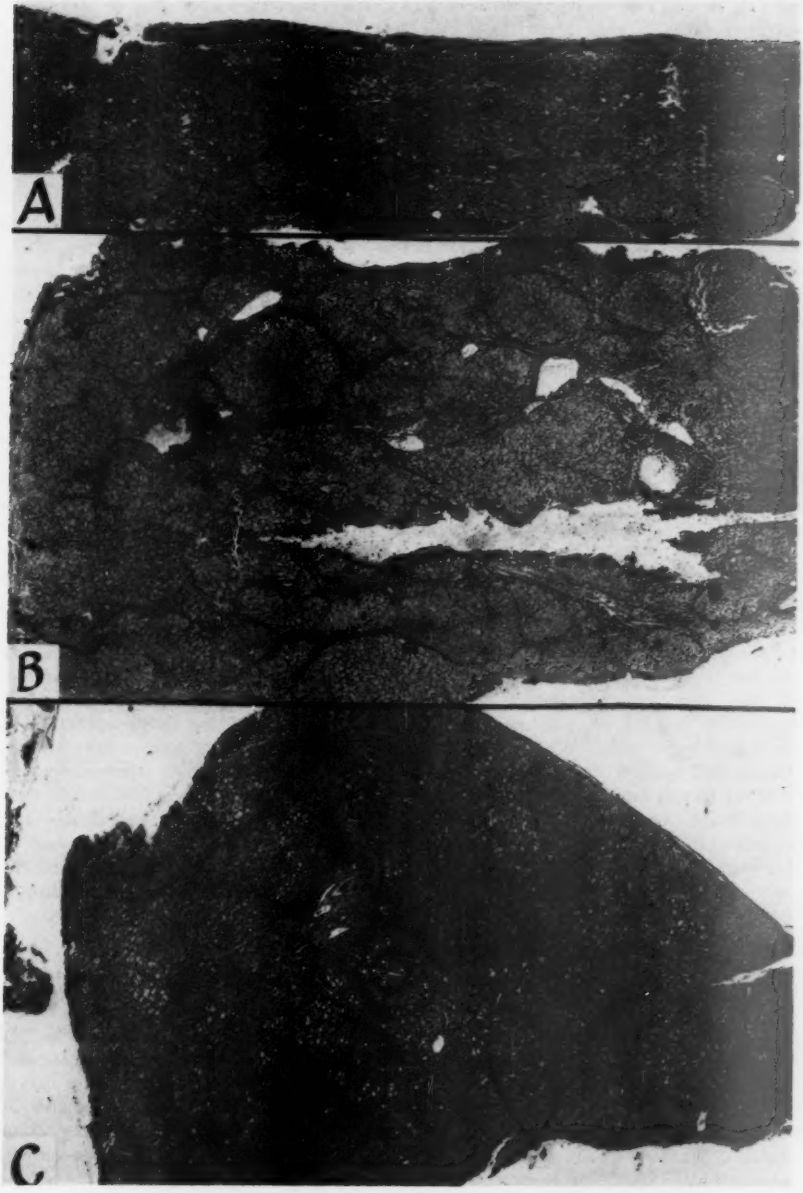


FIG. 3. Liver biopsies obtained during the first, fourth and seventh admissions of case 2. Time intervals between A and B, one and one third years; B and C, two years; C and death, three years.

signs of weight loss. His stools were bulky, weighing 300 to 600 gm. per day, but were not fatty in appearance. On two occasions, quantitative stool fat excretion was 2 and 13 gm. per day. The hemogram and sedimentation rate were normal. His fasting blood sugar was normal, and a two-hour postprandial determination was slightly abnormal. The A/G ratio was 3.6/2.4 gm.%. Blood urea nitrogen, calcium, phosphorus, cholesterol, serum bilirubin, bromsulfalein and phenolsulfonphthalein were all normal. Serial urinary amylases were normal. No pancreatic calcification could be detected in the flat film of the abdomen. A gastrointestinal series, barium enema, small bowel series and cholecystogram were normal except for diverticulosis of the sigmoid colon. A second gastrointestinal series was also normal. Though an obscure malignancy was suspected initially, the discharge diagnosis was chronic pancreatitis, and the patient was treated with pancreatin. His abdominal distress gradually relented over the nine-month period of hospitalization.

The patient was recalled in two months for reëvaluation, at which time he complained of generalized pruritus and intermittent upper abdominal postprandial pain. Hemogram, sedimentation rate, urine amylase and serum bilirubin were still normal. A postprandial blood sugar was abnormal, as was a carotene absorption test. Fecal fat excretion was 19 gm. per day, and the stools were again bulky and foul, weights ranging from 180 to 480 gm. per day. A gastrointestinal series was again normal, but now the gall-bladder was not visualized after either oral or intravenous dye studies. The patient was discharged after three weeks with diagnoses of chronic cholecystitis and pancreatitis, and was scheduled to return for cholecystectomy.

Upon his return one month later the patient was jaundiced. The jaundice developed rapidly over a period of two weeks. His pruritus had persisted unabated since discharge. Hepatomegaly was also evident for the first time. His sedimentation rate was now 34 mm. per hour, and alkaline phosphatase was 46 King-Armstrong units. Cephalin flocculation was normal. Two weeks after admission the patient was explored surgically for obstructive jaundice. An irregular mass was found in the head of the pancreas which was attached to the root of the superior mesenteric vein. The rest of the pancreas was small and indurated. No peritoneal or liver metastases were seen. Whipple's procedure, with total pancreatectomy, splenectomy, and an 80% gastrectomy, was performed. The portion of superior mesenteric vein attached to the tumor was resected, and an end-to-side anastomosis was made with the inferior vena cava. The portal vein was divided in the porta hepatis. The common bile duct was anastomosed to the jejunum, and a Hofmeister closure of the stomach was followed by gastrojejunostomy. Pathologic diagnoses were adenocarcinoma of the head of the pancreas, severe chronic pancreatitis and chronic cholecystitis.

Postoperatively, the patient's blood sugars were in the range of 300 to 400 mg.%, but within three weeks he was reasonably well, though not completely controlled, with 10 to 20 units of insulin daily. Two transient episodes of hypoglycemia occurred, two and two and one-half months after surgery. One month after surgery, recurrent drowsiness and lethargy first became manifest. During the next two months he had at least a dozen episodes, characterized to a variable extent by drowsiness, stupor, agitation and belligerency when aroused, confusion, and disorientation. On one occasion, two months to the day after surgery, the patient was found to be combative, disoriented and lethargic, with bilaterally positive Babinski's reflexes. The blood ammonia was 284 μg.%, and the blood sugar was 149 mg.%. The episode cleared spontaneously. Another recurrence of this severity took place five weeks later, and the patient was given arginine hydrochloride, 50 gm. intravenously, for the first time. Improvement followed and persisted for the next seven days, at the end of which time he was discharged on a 30-gm. protein intake. A serum protein at this time

showed an A/G ratio of 2.7/2.5 gm.%. His weight at discharge was 124 pounds, compared to 142 pounds on admission four months previously.

Within three weeks of discharge the patient was admitted to his local Veterans Administration hospital because of weakness, ascites and edema. His weight was 151 pounds. He was treated with chlorothiazide, with prompt diuresis, losing 40 pounds in two weeks. For one and one-half months while on a 30-gm. protein diet, he seemed to be much improved, and received weekly passes to go home. At the end of this interval he had an episode of stupor, agitation and belligerency when aroused, confusion, and disorientation. The blood sugar was 320 mg.%. Two days

TABLE 6

Sequence of Changes in Case 3 during Several Episodes of Protein or Hypoglycemic Coma, Contrasting Responses to Intravenous Arginine and Glucose, Respectively

Days Since Adm.	Time	Mental State and Treatment
		Protein Pre-Coma
1	5:30 p.m.	Admission. Lethargic, very belligerent, incoherent, BS 98, Cl 111, CO_2 22, BUN 19
	9:10 p.m.	Arginine HCl, 50 gm. IV over 6 hrs.
2	2:00 a.m.	Answers questions rationally, moaning
	5:00 a.m.	Alert
	8:00 a.m.	Alert, Cl 105, CO_2 25
		Protein Coma
5	7:00 a.m.	Poor response, agitated and belligerent when touched
	9:00 a.m.	Does not respond, light coma
	11:00 a.m.	Unresponsive, BS 280, serum acetone negative, $MgSO_4$, 4 gm. over 3½ hrs. reg. insulin (RI), 5 u.
	2:00 p.m.	Unresponsive
	4:20 p.m.	Light coma, arginine HCl, 50 gm. IV over 8 hrs.
	6:00 p.m.	Slight response
	10:00 p.m.	No change
6	12:45 a.m.	Responds to spoken word
	2:15 a.m.	Arginine HCl, 50 gm. IV over 6 hrs.
	8:00 a.m.	Alert, drinking fluids, BS 210, RI 5 u.
	2:00 p.m.	Alert, out of restraints
		Combined Hypoglycemic and Protein Coma
20	8:00 a.m.	Drowsy, eating poorly, RI 5 u.
	6:00 p.m.	Lethargic, not belligerent, RI 5 u.
	7:00 p.m.	Unresponsive
	9:00 p.m.	Comatose, BS 15, poor response to glucose, 25 gm. IV
	10:00 p.m.	Comatose, arginine HCl, 100 gm. IV over 13 hrs.
21	12:30 a.m.	Responds slightly
	3:00 a.m.	Voided
	7:00 a.m.	Drowsy, coöperative, voided, BS 91.
	8:00 a.m.	Ate breakfast, responses slow
		Hypoglycemic Episodes
24	7:00 a.m.	Patient confused, RI 5 u., again at 5:00 p.m.
	9:30 p.m.	Perspiring, comatose, BS 25, prompt response to glucose, 25 gm. IV, drank 400 ml. o.j.
25	8:00 a.m.	Alert, eating alone, RI 5 u., again at 5:00 p.m.
	8:30 p.m.	Responding poorly, eyes open, drank 120 ml. o.j., prompt recovery
26	1:30 a.m.	Moaning loudly, responding poorly
	2:00 a.m.	Glassy-eyed
	7:30 a.m.	Responding poorly, BS 30, prompt response to glucose, 25 gm. IV
	5:00 p.m.	Ate supper alone
27	8:00 a.m.	Alert, ate breakfast alone, BS 181, RI 5 u.
	5:00 p.m.	Ate supper, RI 2 u.
	8:45 p.m.	Comatose, BS 30, prompt response to glucose, 15 gm. IV.

previously, when he was asymptomatic, a blood sugar of 35 mg.% had been recorded. The present episode was interpreted as one of protein precoma, and he was transferred to this hospital for the final time.

On arrival here he was incoherent, very belligerent and lethargic. He received arginine hydrochloride, 50 grams intravenously, and cleared mentally the next day. His weight was 103 pounds; and his A/G ratio 2.4/3.7 gm.%. A transient hyperchloremia (Cl 111, CO_2 22) was recorded the first day, values being normal thereafter. The patient seemed to be unable to tolerate 30 gm. of protein per day, having another episode of protein coma on the fifth day, which responded again to arginine. He was thereafter limited to 20 gm. of protein per day. He seemed to show increasing sensitivity to insulin as well as to protein, requiring less than 10 units of insulin per day, and having several hypoglycemic episodes. The sequence of mental changes during his main episodes of protein coma and of hypoglycemia, showing the responses to arginine and glucose, is given in table 6.

During the last four days of his life he seemed to change from a state of lethargy to one of catatonia. He was unresponsive but not unconscious. He withdrew from pain on light touch but would respond to no one, including his wife. Arginine was ineffective in large dosage. His blood sugars were normal or elevated. A protein level gave an A/G ratio of 1.8/2.5 gm.%. The last day, the thirty-fourth day after admission, he began to have seizures, at first petit mal in type, but later major convulsions. These were almost continuous during the last six hours before death.

Autopsy: The body weighed 101 pounds. Edema, congestion and bronchopneumonia were prominent in the lower lobes of both lungs. The liver weighed 810 gm. and contained no metastases, showing only diffuse mild biliary cirrhosis and one benign cholangioma. The common bile duct anastomosis was intact and patent, as was the connection of the superior mesenteric vein to the inferior vena cava. There were no evidences of metastases. The brain examination was normal.

Final Diagnoses: Adenocarcinoma and chronic inflammation of the pancreas, resected. Recurrent protein encephalopathy due to portal-systemic shunt. Postpancreatectomy diabetes mellitus. Recurrent hypoglycemia due to insulin. Mild biliary cirrhosis. Bronchopneumonia.

Discussion

Clinical Sequences: The recurrent manifestations of protein sensitivity displayed by our patients fit the patterns so elegantly described by Summerskill and co-workers [1] in their paper, "The neuropsychiatric syndrome associated with hepatic cirrhosis and an extensive portal collateral circulation." Our patients had perhaps the worst possible combination of predisposing circumstances: the combination of cirrhosis, an end-to-side portacaval shunt and an extensive gastrectomy. This undoubtedly accounted for their exaggerated sensitivity to nitrogenous substances, above and beyond that seen in the ordinary shunt patient. In each instance the shunt encephalomyelopathy occurred after the complete combination of anatomicophysiologic insults had taken place.

The first patient had no neuropsychiatric symptoms for three years during the coexistence of cirrhosis and a Billroth II gastrectomy. After the addition of the portacaval shunt he promptly manifested symptoms of shunt encephalopathy; however, two years elapsed before the onset of his

paresis and then paralysis. In his case there is reason to correlate the final occurrence of total paralysis with an episode of coma. The first appearance of frank paralysis followed an episode of deep coma, although in retrospect he had been having progressive difficulty. Seven months later he still had a little movement of his legs, feet and toes, but immediately after another episode of deep coma his paralysis was complete and permanent. The second patient had no neuropsychiatric symptoms for two years after a portacaval shunt successfully eliminated his intractable ascites. Within six months after the gastrectomy was added he had his first episode of protein coma; however, two years elapsed before the development of spastic paralysis. Both patients claimed to eat heartily and to tolerate meats and other foods well at times during this interval. Once the sensitivity to protein developed, it seemed to progress until neither patient could tolerate as much as 25 gm. of protein a day. Recurrences of incipient or frank symptoms of precoma or coma became quite common, so much so that in the last several months before death the milder episodes were ignored. At the time that intolerance to oral protein was maximal, the first patient had an episode of incipient precoma following a blood transfusion on one occasion, and several plasma transfusions on two other occasions. This was unfortunately not explored further. There being many other recurrences of similar symptomatology when transfusions were not given, it is difficult to be sure that the association was more than coincidental.

The course of the third patient, who had comparatively mild hepatic disease, was more rapidly progressive. He wasted away quickly and died six and one-half months after surgery, having no evidence of spinal cord involvement, though his terminal episode was marked by convulsions which went unexplained. No metastases from his carcinoma were found at autopsy. He differed from the first two cases in not having portal hypertension and portal-systemic collaterals at the time of surgery. Within one month he manifested his protein sensitivity, which recurred frequently and progressed very rapidly. He also became increasingly sensitive to insulin, experiencing episodes of hypoglycemia which had to be distinguished from those of protein precoma. The response of the hypoglycemic episodes to intravenous glucose was prompt, distinguishing them from the episodes of protein coma in which the response to arginine was delayed. Also, belligerency and combativeness were characteristically his earliest manifestations of protein precoma, but not of hypoglycemia. The initial predisposition was to pass off all of his episodes as hypoglycemia; however, the blood sugar measurements and the unresponsiveness to intravenous glucose made it evident that another variable was involved. The very rapid wasting and deterioration of the patient must be related to his inability to tolerate protein. Prior to surgery he maintained his weight at approximately 142 pounds for about one year despite steatorrhea. After surgery he wasted away to 101 pounds within six and one-half months, and no cancer was found at autopsy to

account for this. Perhaps the rapid course precluded the appearance of the permanent neurologic abnormality observed in cases 1 and 2.

Of incidental interest in the present context was the finding of a persistent hyperchloremia without commensurate hypernatremia in the first two patients. The rise in serum chloride seems to be related to the combined lowering of serum proteins and bicarbonate. We have no ready explanation for the reduction in serum bicarbonate in these patients. Their renal function was apparently normal, and they hyperventilated only intermittently with their episodes of precoma or coma. However, we suspect that they may have been unable to acidify their urine normally, as in cases of renal tubular acidosis, or hyperventilated subclinically.

Also of incidental interest is the fact that the microscopic appearance of the liver, the fibrosis of the pancreas, and the hyalinization of the glomeruli at autopsy examination in case 1 are similar to the findings in kwashiorkor, likewise a state of prolonged protein deficiency.

Response to Arginine: These patients responded very sensitively to arginine. In fact, one could roughly titrate the amount of arginine needed by the mental state of the patient. This led to repeated use of arginine hydrochloride or arginine-glutamate intravenously for the more severe episodes. The first patient received 1,375 gm. of arginine or arginine-glutamate intravenously over a period of one year in the treatment of 13 moderate or severe episodes of precoma or coma. The second patient received 650 gm. of arginine or arginine-glutamate intravenously over a period of five months in the treatment of nine moderate or severe episodes of precoma or coma. The third patient received 400 gm. of arginine or arginine-glutamate intravenously over a period of one month in the treatment of recurrent episodes. Though we have used arginine hydrochloride or arginine-glutamate in large dosage in approximately 40 cases of hepatic coma or precoma, and have seen a significant number of unequivocal responses, particularly among cases of exogenous origin, no other patients have responded so sensitively or so promptly as these.[2]

The value of intravenous arginine in the treatment of episodes of protein coma or hepatic coma is at present highly controversial. We believe this stems primarily from two factors: variability in the patients selected for therapy, and variability in the dosage used. The patient with bleeding esophageal varices who lapses into coma is not likely to respond to arginine if the bleeding cannot be controlled. At the opposite extreme, a similar patient with gastrointestinal hemorrhage and mild precoma whose bleeding stops is likely to recover spontaneously. The patient with very extensive liver destruction and spontaneous hepatic coma is not likely to respond successfully to arginine or any other therapy, whereas the patient with precoma from an exogenous cause is likely to recover spontaneously if the causative factor is removed or corrected. In the various series reported, variability in the underlying hepatic disease, the mental state of the patients, and the

coincident complications undoubtedly contributed greatly to the variable experiences cited and the conclusions drawn. Also, confusion has arisen from the failure to distinguish between the immediate response of the patient to the drug and the ultimate outcome of the illness, which may terminate fatally for a variety of other reasons. In our experience,[2] to be reported later, arginine has been most valuable in patients who are frankly unconscious with hepatic coma due to an exogenous cause. Only infrequently have we seen spontaneous recoveries in such unconscious patients prior to the use of intravenous sodium (or potassium) glutamate or arginine in large amounts.

As with glutamate, the dose of arginine used is critical. Only in the milder cases of precoma, who are apt to recover spontaneously, is as little as 25 gm. intravenously adequate as a rule. Our usual minimal dose is 50 gm., and the necessity for 100 gm. or more is common. Najarian and Harper,[3-5] who reported successful responses with arginine in suitably selected cases, have generally used at least 50 gm. intravenously. Those who have reported little or no success with arginine have generally used less than 50 gm.[6-9]

The response to intravenous arginine in hepatic coma or protein coma is not prompt, like the response of hypoglycemia to glucose. The contrast was evident in case 3, who was having episodes of both hypoglycemic and protein coma. In deep hepatic comas there is characteristically a lag of from 12 to 24 hours before unequivocal evidences of the response to therapy are manifest. In milder episodes the lag is only a few hours.

Patients with protein sensitivity, such as the three detailed in this report, are more apt to recover spontaneously from episodes of protein precoma or coma than is the usual case of hepatic coma. With the possible exception of the first episode of coma observed in case 1, when the patient appeared to be moribund at the time of starting therapy, we cannot claim with assurance that arginine was lifesaving for any one of the episodes of protein coma or precoma in which it was used in these patients, though this might be the case. However, it seemed clear repeatedly that the episode was aborted, the trend reversed and recovery hastened by the use of arginine. As with patients in ordinary hepatic coma who respond to arginine, there seemed little to choose between the acidic arginine hydrochloride and the non-acidic arginine-glutamate. Both were equally effective, precluding the possibility that arginine hydrochloride owes its value to its acidifying effect.

Summary

The occurrence of severe and progressive protein intolerance with recurrent episodes of protein precoma or coma following the combination of cirrhosis, gastrectomy and portacaval shunt has been described in three patients. The gastrectomy appeared to augment the effects of the portacaval shunt. The recurrent episodes of protein precoma or coma responded

sensitively to intravenous arginine in large dosage. The marked and progressive protein sensitivity led to body protein depletion and wasting. A persistent hyperchloremia was correlated with the protein depletion in two of the patients with portal cirrhosis and prolonged courses.

ACKNOWLEDGMENTS

We are grateful to the Central Research Laboratories of General Mills, Incorporated, for providing us initially with crystalline arginine hydrochloride and arginine glutamate, and to Abbott Laboratories for later supplying us with sterile arginine glutamate solution.

SUMMARIO IN INTERLINGUA

Le occurrentia de sever e progressive intolerantia pro proteina con recurrente episodios de precoma o coma proteinic post cirrhosis e gastrectomia in combination con anastomose porto-caval es describite in tres patientes. Quando le sensibilitate pro proteina esseva initialmente establite, illo pareva progreder usque le patiente—e isto valeva in omne le tres casos—poteva tolerar non mesmo le micre quantitate de 25 g de proteina per die. Recurrentia de incipiente o patente symptomas de precoma o coma deveniva satis commun, usque a tal grados que durante le menses terminal le episodios plus leve debe esser ignorate. Le gastrectomia pareva augmentar le effectos del anastomose porto-caval. Le recurrente episodios de precomo o coma proteinic respondeva sensibilemente a arginina intravenose in grande doses. Le tres patientes recipeva 1.375, 650, e 400 g de arginina o de glutamato de arginina per via intravenose in le curso de periodos de 12, cinque, e un mense, respectivemente. Il esseva possibile estimar plus o minus precisemente le quantitate de arginina requirite per evalutar le stato mental del patiente. Nulle del altere patientes con coma o precoma hepatic qui esseva tractate per nos con arginina ha unquam manifestate un responsa similemente sensibile o prompte. Le marcate e progressive sensibilitate pro proteina resultava in le depletion del proteina del corpore con consequente dystrophia. Un persistente hyperchloremia esseva correlationate con le depletion de proteina in duo del patientes con cirrhosis portal e cursos prolongate.

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SHUNT ENCEPHALOMYELOPATHY. II. OCCURRENCE OF PERMANENT MYELOPATHY *

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The reversible acute or chronic recurrent neurologic signs associated with hepatic coma, Eck's fistula, or an extensive portal collateral circulation are well known. So is the coexistence of permanent hepatic and nervous system abnormalities in hepatolenticular degeneration. However, the occurrence of nontransient neurologic findings in isolated patients with liver disease, exclusive of Wilson's disease, has not been so widely appreciated. Little emphasis has been placed upon the development of focal neurologic manifestations, particularly of the spinal cord, though a few instances have been recorded in the literature. Moreover, clinical neuropathologic correlations have been exceedingly scant. Our observation recently of two cirrhotic patients with permanent spastic paraplegia associated with repeated episodes of protein coma which followed the combination of gastrectomy and portacaval shunt prompted this report.

Case Reports

Except for the neuropathologic data, complete summaries of case 1 and case 2 have been presented in the preceding paper. Following are the neuropathologic findings in case 1:

External examination of the brain, spinal cord and peripheral nerve specimen revealed no abnormalities. Serial sections through the cerebral hemispheres, brain stem and cerebellum disclosed no significant alterations. Serial sections through the spinal cord showed a slight whitish discoloration in the dorsal portion of the lateral columns bilaterally, beginning at the level of the cervical enlargement and becoming slightly more pronounced as the cord was sectioned caudally.

Sections for *microscopic examination* were taken from the motor cortex, sensory cortex, hippocampus formation, basal ganglia, thalamus, hypothalamus, midbrain, pons, cerebellum, medulla, and all levels of the spinal cord. Both transverse and longitudinal sections were made of the spinal cord and peripheral nerve. Stains employed on paraffin-embedded blocks included hematoxylin and eosin, Nissl, Holzer, Weil and Bielschowsky. Fresh tissue was stained for fat by the Sudan III and Oil Red O methods.

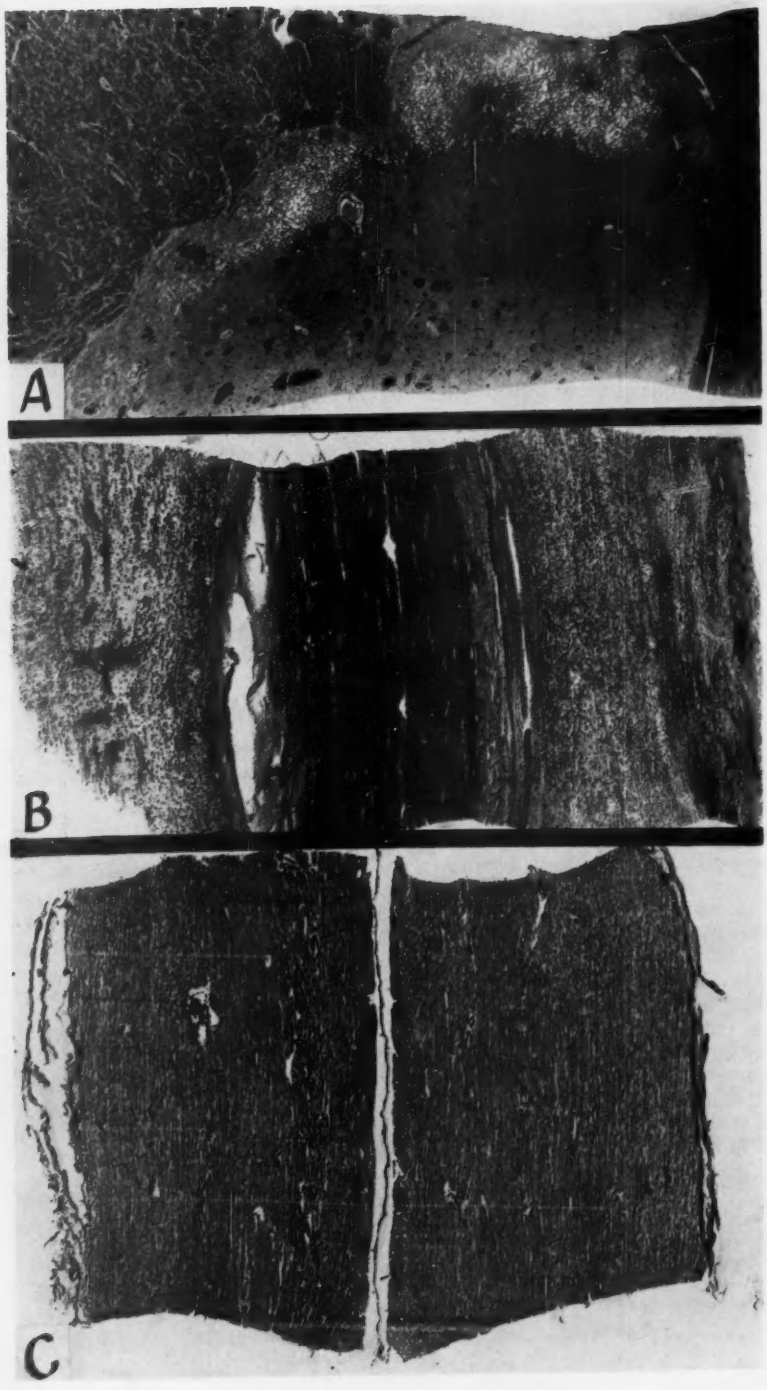
In the cerebral hemispheres the meninges and blood vessels were normal. The cortical neurons showed no appreciable alteration. However, scattered through the

* Received for publication October 14, 1959.

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A
B
C

deeper layers of the cortex and the subcortical white matter were typical Alzheimer's type II glial cells, possessing a vesicular nucleus outlined by a prominent nuclear membrane and containing one or more large clumps of chromatin. There was no evidence of demyelination in the subcortical white matter. Sections through the insular cortex and corpus striatum revealed many Alzheimer's type II glial cells in the caudate nucleus and putamen. A small area of spongy degeneration with vacuolation and shrinkage of tissue was seen in the putamen (figure 1A). There was little fibrous glial reaction around the area, and no evidence of macrophage activity. No striking neuronal alterations were evident. Nissl staining demonstrated some pyknosis of the nuclei of the neurons of the subthalamic nucleus. Sections through the pons revealed a moderate number of Alzheimer's type II glial cells. Sections through the cerebellum showed a striking proliferation of Alzheimer's glial cells in Purkinje's cell layer and, to a lesser extent, in the granular cell layer and the subcortical white matter. No neuronal change was seen. Sections through the medulla revealed a few fresh petechial hemorrhages in the area postrema.

Sections through the spinal cord showed a general thickening of the leptomeninges, with increase in fibrous tissue and depositions of both free and macrophaged blood pigment within the meningeal tissue. Amyloid bodies were scattered throughout the parenchyma. The small blood vessels showed a moderate degree of medial fibroblastic proliferation with occasional medial hyalinization. There were general diminution of interfascicular oligodendrogliacytes and proliferation of the previously described Alzheimer's type II glial cells both in the white matter and in the anterior and posterior horns. Myelin and fat stains demonstrated marked demyelination in the lateral columns bilaterally and in the medial surfaces of the anterior columns, corresponding to the anatomic location of the lateral and ventral corticospinal tract (figure 2). This process commenced at the level of the cervical enlargement and became more pronounced caudally. Longitudinal sections through the involved areas revealed heavy depositions of phagocytosed globules of free fat (figure 1B). Longitudinal sections through the same area stained for axis cylinders disclosed neither abnormality nor diminution in number (figure 1C). A glial stain failed to reveal proliferation around the region of demyelination. There was some capillary prominence within the lesion. Very occasionally there was a slight to moderate infiltration by small round cells with darkly staining nuclei in the walls of the small blood vessels in this area. Occasional demyelination of both posterior and anterior rootlets was seen in the region of the lumbosacral cord and the cauda equina.

Sections both transverse and longitudinal of the peripheral nerves revealed no pathologic alteration.

In summary, the most consistent general finding was the widespread and profuse proliferation of Alzheimer's type II glial cells. Save for the one area of spongy degeneration in the putamen, neuronal alterations were conspicuous by their absence. The striking feature of the case from a neuropathologic standpoint was the selective demyelination in the spinal cord limited to the pyramidal tracts. The involvement extended no higher than the cervical cord, and became progressively more marked caudally. Pyramidal tract demyelination could not be demonstrated in the medulla, pons, cerebral peduncles or internal capsule. The longitudinal sections of spinal cord demonstrating severe demyelination in the presence of morphologically intact axons also indicate that the lesion was a primary demyelination.

FIG. 1. A. Spongy degeneration in putamen of case 1. B and C. Specially stained longitudinal sections through spinal cord, showing phagocytosed globules of fat in demyelinated area (B) and preserved axis cylinders (C).

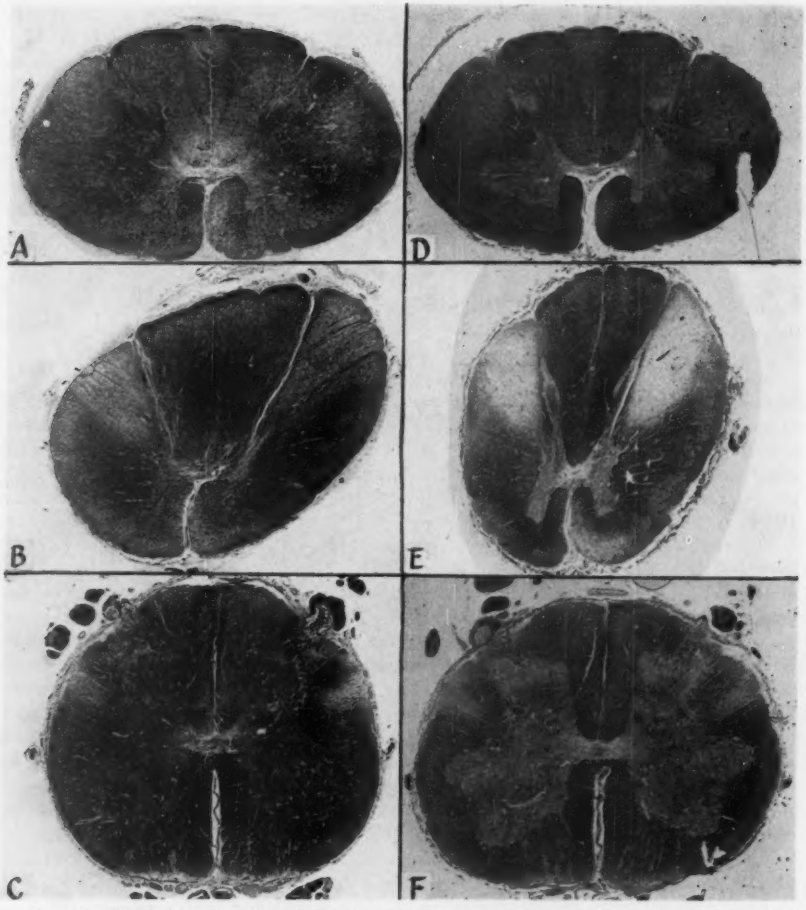


FIG. 2. Weil (A, B, C) and luxol fast blue-hematoxylin eosin (D, E, F) stained sections of cervical, dorsal and lumbar regions of spinal cord in case I, showing pyramidal tract demyelination.

CASES FOUND IN SURVEY OF LITERATURE

We were able to find two clear-cut case reports demonstrating spinal cord demyelination in patients with portal-systemic collaterals.

The *patient of Leigh and Card* [1] was a 50 year old man who had had several hematemeses over a five-year period. At his last hospitalization he had edema, ascites, hepatomegaly, splenomegaly, anemia, leukopenia, thrombocytopenia and esophageal varices. A total serum protein was 6.4 gm.%. In addition, his memory was impaired, his speech was slurred, and his emotions were labile. The cranial nerves were normal. His right arm was weak, and his legs were weak, unsteady and spastic. Vibration

and position senses were diminished. He also had a parkinsonian-like tremor and urinary incontinence.

During hospitalization the patient's tremor became severe, and he had a period of high fever. An episode of spontaneous coma was followed by spontaneous recovery, only to be followed later by a recurrence of coma, and death. At autopsy he had marked varices and typical portal cirrhosis. The liver weighed 1,125 gm., the spleen, 730 gm. The brain weighed 1,570 gm. and showed scattered spongy degeneration of the cerebral cortex and basal nuclei with Alzheimer's type II glial cells. The lateral and posterior spinal columns were demyelinated.

Comment: The patient had hepatolenticular degeneration, not Wilson's disease, in addition to severe cortical damage and glial reaction in the midbrain and medulla. The spinal cord showed demyelination of the posterior and lateral columns. Thus, lesions widely scattered throughout the central nervous system were demonstrated. The cirrhosis was extensive, as were the portal-systemic collaterals.

The patient of Baltzan et al.[2] was reported as an example of chronic portohepatic encephalopathy. He was a 50 year old male diabetic who, four years prior to his final illness, gave a history of blurred vision, diplopia, circuitous gait, dysarthria, and spells of stiffening and unconsciousness associated with numbness and weakness of the left leg. Examination at that time revealed dysarthria, a left facial weakness, weakness of the left leg, bilateral ankle clonus, left Babinski's and left Hoffmann's signs, an intention tremor and rebound phenomenon of the arms, poor coördination, an enlarged spleen, and clubbing of his fingers. Moderate hepatic dysfunction was evident from the laboratory tests: serum bilirubin, 1.0 mg.% in one minute and 2.3 mg.% total; bromsulfalein retention, 21% in 45 minutes; cephalin flocculation, 2 plus in 48 hours; thymol turbidity, 11 units; alkaline phosphatase, 10 Bodansky units; albumin, 3.6 gm.%, and globulin, 4.0 gm.%; serum cholesterol, 188 mg.%; prothrombin concentration, 36%, with little response to vitamin K. The fasting blood sugar was 142 mg.%. A serum iron was 166 μg.%, and ceruloplasmin, 23 mg.%. The pattern of amino acids on chromatography of the urine was similar to that in Wilson's disease, but the amounts were not increased. An electroencephalogram was diffusely abnormal, and a pneumoencephalogram showed bilateral cortical atrophy.

During the four-year interval leading to his final hospitalization the patient's symptoms were intensified. He was semicomatose on admission and commonly stuporous thereafter. Dysarthria was very severe. The neurologic examination was essentially similar to that seen before. Liver function tests were again abnormal, the A/G now being 2.6/4.7. His left eye was infected and required enucleation. Over a two-month period he deteriorated progressively and died, having been ill for six years with progressive motor, cerebellar and mental deterioration.

At autopsy, ascites was present. The liver weighed 1,000 gm., the spleen, 400 gm. A massively dilated portal vein was obstructed by a large calcified plaque. The liver showed minimal scarring of the postnecrotic type. Tissue copper analyses were low. The brain weighed 1,185 gm. and showed scattered spongy degeneration in the putamen, globus pallidus, midbrain and cerebellum. Alzheimer's type II glial cells were prominent generally, and there was patchy laminar loss of nerve cells in the cortex. The pyramidal tracts were demyelinated, thought by the authors to be a secondary degeneration.

Comment: The patient presented many of the clinical and pathologic features of Wilson's disease but could not be so classified. He also had many features of portal-systemic encephalopathy; however, his course was progressive and his neurologic findings were permanent. The spinal cord abnormalities were a prominent component of his illness. In view of the finding of preserved axone cylinders in our case 1, we suspect the pyramidal tract demyelination was primary rather than secondary in this patient, as suggested. The portal vein occlusion was undoubtedly of primary importance in the development of his portal-systemic collateral.

A third, somewhat similar case, reported by Inose,[3] is of interest, though no mention was made of spinal cord pathology. The patient was one of four with "hepatocerebral degeneration," which Inose distinguished from Wilson's disease. The one case presented in some detail was a 47 year old alcoholic woman whose illness lasted for four years. She had had frequent brief episodes of unconsciousness. Tremors of her hands and head, dysarthria, unsteadiness of gait, progressive loss of memory and poor judgment were her primary symptoms. In addition to her tremors, she had athetoid movements, poor coördination of her limbs and trunk, hyperactive knee and ankle jerks bilaterally, and positive Babinski's reflexes bilaterally. The mental and neurologic symptoms progressed with the recurrent episodes of coma. The other three cases had similar relapsing comas, with progressive cerebellar and pyramidal tract findings. The autopsy findings of all four cases are reported as one, so one cannot isolate the pathologic processes pertaining to the only case reported in detail. However, the livers were atrophic and fatty, the average weight being about 700 gm., and were probably cirrhotic. In the brains there was scattered spongy degeneration of the putamen, globus pallidus, thalamus, nucleus ruber and cerebral cortex. Alzheimer's type II cells were prominent.

Discussion

Neuropathology: Gross and microscopic neuropathologic alterations in the central nervous system associated with liver disease, particularly cirrhosis, have been described in great detail by many authors.[4–9] The literature was reviewed by Brown[9] in a recent monograph. In brief, gross lesions may consist of cavitation in the region of the basal ganglia, atrophy of the basal ganglia, and cortical atrophy. Microscopic alterations have

been noted to involve the neurons, glia and myelin. The neuronal changes described include those of acute damage, consisting of such phenomena as swelling and fragmentation of the cell body and cellular tortuosity. The extreme form of neuronal alteration consists of complete degeneration and disappearance of neurons and myelin which, when extensive, produces gross atrophy and cavitation of gray matter, and the microscopic picture of spongy degeneration of the cerebral cortex, basal nuclei, etc. The outstanding glial alteration is the presence in profusion of a greatly enlarged astrocyte with a large vesicular nucleus and prominent nuclear membrane. This is commonly referred to as Alzheimer's type II glial cell. However, its presence is not constant in cases of liver disease, nor is it limited to such diseases. In addition to the presence of Alzheimer's cells, other less striking forms of glial alterations have been described which are similarly nonspecific. Loss of myelin has been noted frequently, and may be diffuse, patchy or perivascular. It is usually most pronounced in the deepest lamina of the cortex and the immediately subjacent white matter. It should be emphasized once again that none of these changes is specific for liver disease.

Lenticular degeneration in combination with cirrhosis is associated first of all in our minds with Wilson's disease. However, it is now well recognized that many—and perhaps, in absolute numbers, most—of the cases of cirrhosis with hepatolenticular degeneration are not examples of Wilson's disease. More often than not, the lenticular lesion is but one aspect of widespread brain involvement. This is also true of Wilson's disease, in which the neuropathologic changes have typically not been limited to the basal ganglia.

Compared to the remainder of the nervous system, the spinal cord has received little attention, either clinically or pathologically. According to Wilson, the spinal cord is usually normal in hepatolenticular degeneration; however, as long ago as 1930 Von Braunmuhl [4] reported demyelination in the spinal cord. Brown [3] examined the spinal cord in only five of his 42 cases of fatal hepatic coma, and mentions that two cases showed "demyelination of a mild degree in the lateral columns," though no correlated clinical symptoms were noted. The distinguishing features of the cases reviewed in this report are the spinal cord findings. The case of Leigh and Card [1] manifested general nervous system involvement of long duration. Postmortem examination was consistent with the clinical neurologic findings in that areas of spongy degeneration were noted in the cerebral cortex and basal ganglia, along with widespread proliferation of Alzheimer's glial cells and microglia and fibrous gliosis in the cerebral white matter and caudate nucleus. Myelin degeneration was demonstrated in the spinal cord, involving the lateral columns in the thoracic and lumbar segments and the posterior columns in the cervical and thoracic segments. No mention was made of the status of the axons in the demyelinated areas of the cord.

The case reported by Baltzan and co-workers [2] had permanent neurologic damage over a prolonged period, with widespread involvement. As would

be expected, the central nervous system showed diffuse alterations on postmortem examination. The most severely affected structure was the cerebral cortex, which contained lesions in a patchy laminar distribution within the fourth and fifth layers, most intense in the motor areas. There were also a number of chronic neuronal alterations, such as pyknosis of nuclei, cellular shrinkage, and elongated dendritic processes. Moreover, neuronal changes were seen in the basal ganglia, midbrain and cerebellum. Alzheimer's cell proliferation was observed in most areas. There was spongy demyelination in the superior cerebellar peduncles. The spinal cord showed demyelination of the crossed and uncrossed pyramidal tracts. Again, no mention was made of the axons in the involved areas of the cord.

The brain abnormalities in the cases of Inose [3] were essentially similar to the previous two. No allusion was made to the spinal cord.

Our two cases resemble those above in that they demonstrated clinically permanent focal neurologic abnormalities in association with hepatic disease and portal-systemic shunting. With the exception of the episodes of coma, however, clinical neurologic involvement in our patients was almost completely limited to the spinal cord. The one case autopsied showed brain changes commonly associated with liver disease, but to a much lesser extent than those above, particularly with reference to neuronal changes. However, the demyelination of the spinal cord was striking. The presence of intact axis cylinders in the areas of severe spinal cord demyelination has not apparently been recognized previously. We assume that the anatomic lesion in our second, unautopsied case was similar to that in the first.

Etiologic Factors: The critical factor in the production of either transient or permanent encephalopathy or myelopathy is most likely the portal-systemic shunting of blood around the liver, or through the liver but around the hepatic cells, rather than the liver disease per se. Patients without liver disease but with Eck's fistula may have symptoms of protein or ammonia intoxication. Case 3 of the preceding report, who manifested marked protein sensitivity, had only mild biliary cirrhosis anatomically, and practically no measurable hepatic dysfunction.

Of the cases with permanent myelopathy described herein, our two patients and the patient of Leigh and Card had advanced cirrhosis. However, the patient reported by Baltzan and co-workers had minimal cirrhosis anatomically, but massive dilation of the portal vein, which was obstructed by a large calcified thrombus. We must conclude that the common denominator in these cases of permanent myelopathy was portal-systemic shunting around the liver.

What produces the transient or permanent nervous system damage is unknown, though the lesions apparently result from a metabolic disturbance. There is good reason to believe that some nitrogenous derivative or breakdown product of protein, ordinarily removed or modified by the liver, is the noxious agent, in view of the precipitation of symptoms by excessive protein and the benefits of protein restriction. Attributing these effects

entirely to ammonia seems to us an oversimplification. In view of the toxic effect of arginine-deficient amino acid mixtures,[10] and the almost specific action of arginine in reversing this toxicity, as well as the nonpermanent symptoms of shunt encephalomyelopathy, an imbalance of certain amino acids must be considered as one possible etiologic mechanism.

Nutritional deficiency was suspected by Leigh and Card as a cause of the permanent spinal cord changes, in view of the analogous cord changes reported in various nutritional disturbances. This is a possibility one cannot ignore in the cases that gradually develop permanent cord damage after a prolonged interval of protein sensitivity and protein restriction. However, patients with portacaval shunts whose nutrition is entirely normal may manifest transient shunt encephalomyelopathy, and they seem to differ from those with permanent damage only in the duration and frequency of episodes. Vitamin B_{12} deficiency also seems an unlikely cause, in view of the absence of hematologic findings specifically indicative of pernicious anemia, and the progression of the disease in case 1 while he was receiving crude liver extract and, later, massive doses of the pure vitamin.

The exact significance of the gastrectomy in our two patients is difficult to assess, though it seems likely that the absence of the stomach acted primarily as an intensifier of the underlying defect, in view of the fact that the other patients with shunt myelopathy reviewed above had not had gastrectomies. In our two patients, the combination of shunt and gastrectomy seemed necessary to start the train of events. In a patient reported by Magnum et al.,[11] a shunt sufficient to prevent recurrent hematemesis existed for four years without objective evidences of shunt encephalomyelopathy; however, with the addition of a gastrectomy for intractable peptic ulceration, the patient developed typical recurrent manifestations of protein sensitivity after one month. This patient had been controlled for one year on a 40-gm. protein diet at the time of the report. It would be of great interest to reëxamine the patient at this time for evidences of permanent spinal cord damage.

Classification of Shunt Encephalomyelopathies: It is useful to attempt a unification of the various neuropsychiatric syndromes associated with hepatic disease or portal-systemic shunts. The many variants one sees may be segregated into four broad groups:

1. Acute encephalomyelopathy.
2. Acute recurrent encephalomyelopathy.
3. Chronic recurrent encephalomyelopathy.
4. Chronic permanent encephalomyelopathy.

The first, or *acute,* group is composed of the patients with the classic picture of hepatic coma, an illness of fairly rapid onset and short duration. If the episode is severe, death is the rule; however, the patient may recover and have one or two recurrences at a later date. The second, or *acute recurrent,* group includes the patients having more than one but not more than a few

distinct episodes of hepatic coma or precoma, of variable length and severity.

The third, or *chronic recurrent,* group includes patients of the type described by Summerskill and colleagues.[12] They have many recurrences or prolonged persistence of mental, emotional and neurologic abnormalities over a period of years, yet their findings are reversible and controllable with suitable therapy. The fourth, or *chronic permanent,* group includes patients of the type summarized in this report, who have permanent organic central nervous system damage, often resulting in focal neurologic findings, as in the case of lenticular degeneration or pyramidal tract demyelination.

For all groups the predominant involvement may be in one area of the central nervous system to the exclusion of another. Thus, for example, the manifestations may all be of an encephalopathy in one patient, or of myelopathy in another. Most often, however, as one would expect with a blood-borne metabolite, a mixture of findings is evident, and the term "encephalomyelopathy" is most appropriate.

The presumption is that all groups have a common etiologic mechanism, the clinical variations observed resulting from variations in (1) the frequency of ingestion of the noxious agent (or agents), (2) the concentration of the noxious agent, (3) the duration of action of the noxious agent, (4) the extensiveness of the portal-systemic shunt, (5) the availability of detoxifying mechanisms, and (6) the efficiency of detoxifying mechanisms. The latter two are in large measure related to the severity of the liver disease.

Summary

The occurrence of permanent spastic paraplegia is described in two patients with cirrhosis who had repeated episodes of protein coma which followed the combination of gastrectomy and portacaval shunt. Pyramidal tract demyelination in the spinal cord, but not in the brain, was demonstrated in the first case. Two other documented case reports of patients having spinal cord demyelination in association with portal-systemic shunting were found in a survey of the literature; however, these patients had the findings of hepatolenticular degeneration, but not Wilson's disease, in addition to the cord changes.

Both of our patients had marked protein sensitivity which progressed with time, so that body protein depletion and wasting were inevitable. Gastrectomy probably acted primarily as an intensifier of the effects of the portacaval shunt. The spinal cord lesion is believed to be a metabolic effect of some protein breakdown product ordinarily removed or modified by the liver but, in these cases, shunted around the hepatic cells.

An attempted unification of the various neuropsychiatric syndromes associated with portal-systemic shunts or hepatic disease resulted in the segregation of the many variants into four broad groups: acute, acute recurrent, chronic recurrent, and chronic permanent encephalomyelopathy.

Summario in Interlingua

Le occurrentia de permanente paraplegia spastic es describite in le casos de duo patientes con cirrhosis qui habeva repetite episodios de coma proteinic post gastrectomia in combination con shunting porto-caval. Dismyelination del tractos pyramidal in le medulla dorsal sed non in le cerebro esseva demonstrate in le prime del duo casos. Duo altere documentate casos de patientes con dismyelination in le medulla dorsal in association con shunting porto-general esseva trovate in le curso de un scrutinio del litteratura, sed in ambe iste casos le patientes manifestava degeneration hepato-lenticular in ultra de lor alterationes de medulla dorsal, sed non morbo de Wilson.

Ambe nostre patientes habeva marcate grados de sensibilitate proteinic. Isto progredeva in le curso del tempore, e depletion del proteina del corpore e atrophia esseva inevitabile. Il es probabile que le gastrectomia ageva primarimente como un intensificator del effectos de shunting porto-caval. Es opinate que le lesion del medulla dorsal es un effecto metabolic del un o del altere producto del decomposition de proteina que es ordinarimente eliminate o modificate per le hepate sed que in casos del typo hic considerate non attinge le cellulas hepatic.

Le essayo de categorisar le varie syndromes neuropsychiatric que occurre in association con shunting porto-general o morbo hepatic resultava in le combination del numerose variantes in quatro gruppos major. Istos es le casos de encephalomyelopathia (1) acute, (2) acute recurrente, (3) chronic recurrente, e (4) chronic permanente.

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PSYCHOPHYSIOLOGIC MECHANISMS IN HYPERTENSIVE VASCULAR DISEASE*

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In few somatic disorders is the potent impact of emotional stimuli more generally appreciated than in hypertensive vascular disease. Terms such as psychogenic hypertension, neurogenic hypertension, hypertensive personality, vascular stress, repressed hostility and autonomic nervous system lability have developed and are employed commonly. Yet precisely what these terms mean, what the qualitative and quantitative relationships of the emotions to blood pressure are, and what significant contributions to understanding the basic mechanisms of hypertension are made by the study of psychological forces, comprise questions which have not been answered in any systematic fashion. It is little wonder, therefore, that most investigators are inclined to ignore the psychologic parameter in their studies, while the clinician is constantly frustrated by the evidence of the impact of emotional forces on blood pressure which is always before him, yet seemingly so little under his control and so defiant of his understanding. Yet when one cuts through the speculation and wishful thinking, a number of facts are available which do lend themselves to organization and can contribute to our understanding of the over-all problems of etiology, course and management of hypertensive vascular disease.

The available facts can best be stated as answers to five hypothetic questions which define the problems that trouble clinicians and investigators whenever the effects of emotional stimuli on the blood pressure are discussed. They are representative of those with which this author has dealt repeatedly during a decade of experience in conducting medical clinics and teaching rounds with hypertensive patients, and are as follows:

1. How do the emotions result in blood pressure change?
2. Is there a unique and specific "hypertensive personality"?
3. Can hypertensive vascular disease be caused "purely" by emotional stimuli?
4. Is there evidence of aggravation of preëxisting hypertensive vascular disease by emotional stimuli and, if so, why in some individuals and not in others?
5. Is psychotherapy effective? Can it "cure"?

* Received for publication December 4, 1959.

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It is the purpose of this review to attempt answers to these questions insofar as our present state of knowledge permits, to point out in what areas our information is fragmentary, poorly documented or purely speculative, and to define the limitations which the data presently available place on our reasoning.

1. How Do Emotions Result in Blood Pressure Elevation?

A. *Neurohumoral Mechanisms:* Since Cannon's studies in animals,[11] it has been assumed that elevation of blood pressure due to anxiety is mediated through autonomic nervous system activity, which induces vasoconstriction and tachycardia through its sympathetic component. This neurogenic pathway came later to be considered the prime mediator of the physiologic concomitants of anxiety, particularly as concerned changes in blood pressure,[2] and "psychogenic" became synonymous with "neurogenic." However, considerable evidence has accumulated that anxiety also can affect blood pressure through strictly humoral pathways. For instance, Ferris and co-workers record instances where the administration of tetraethylammonium chloride (TEAC) to a patient demonstrating elevation of blood pressure secondary to noxious stimuli will on one occasion lower the blood pressure markedly, while on another occasion, closely related temporally, cause little if any fall.[24] Since TEAC produces a ganglionic blockade and eliminates sympathetic tone, the assumption seems justified that failure to cause a fall of blood pressure with TEAC indicates that the elevation is caused by a humoral mechanism. This assumption has been further supported by the demonstration that in several forms of hypertension which are clearly humoral—pheochromocytoma,[54] unilateral renal ischemia,[9] toxemia of pregnancy and acute glomerulonephritis[24]—TEAC administration frequently does not produce a fall in blood pressure, and occasionally results in a rise. Furthermore, Brust has demonstrated that the rise in blood pressure resulting both from circulating noradrenalin and adrenal cortical steroids is unaffected, or actually can be potentiated, by TEAC.[72, 10] An increase in vascular tone produced by steroids and ACTH can be shown directly.[17] Both circulating noradrenalin and adrenal corticosteroids are humoral agents which can be evoked by noxious stimuli, and consequently are potential mediators of increased vasoconstriction and elevation of blood pressure following anxiety.

There are undoubtedly many additional humoral agents with physiologic vasoconstrictor activity. Among them are vasopressin, hypertensin, and perhaps other polypeptides. The fact that a variety of noxious stimuli may release activators of plasminogen suggests that plasmin may play a role in the formation of such polypeptides.[39] It has indeed been demonstrated that trypsin, which resembles plasmin, may hydrolyze α-2 globulin to a specific tetradecapeptide which, in turn, is split by renin to release hypertensin I.[65] Thus, a number of humoral pathways, independent of the autonomic nervous

system yet nevertheless comparatively rapid in the production of a physiologic change, are available which can respond to noxious stimuli.

Some evidence does in fact exist to suggest actual diminution of the activity of the sympathetic nervous system in the hypertensive individual. For instance, Mirsky et al. have determined the response of the blood sugar to the intravenous injection of 0.1 unit/Kg. of insulin in hypertensive and normotensive individuals. They noted that the return of the blood sugar to control levels was retarded in the hypertensives. Since, in the absence of hepatic or endocrine impairment, restitution of the blood sugar following hypoglycemia is primarily dependent upon the responsiveness of the sympathetic nervous system, the data were interpreted to indicate a decreased responsiveness of this system. It was further suggested that such a decreased sympathetic tonus might relate causally to hypertension, since it would result in an increase in sensitivity of the arterial tree to circulating pressor agents, a postulate which is supported by the many observations of the "sensitization of denervation." [40] If noradrenalin is considered to represent the peripheral neuromediator of sympathetic nervous activity, as von Euler believes,[71] several recent observations are in line with Mirsky's hypothesis. Sundin has demonstrated that the increase in urinary excretion of noradrenalin elicited by tilting an individual into the upright position is greater in normotensives than in hypertensives, thus indicating that orthostatic reflexes actually are inhibited in the latter state.[66] Hickler and co-workers recently have confirmed this observation.[34] Furthermore, Møller et al. have demonstrated not only that noradrenalin excretion in the urine is significantly less in hypertensive individuals as a group, but also that its level within a group of patients with hypertension is inversely related to the level of the blood pressure.[42] The observations of Møller and his associates, however, are at odds with those of many other investigators, who find no significant difference between normals and hypertensives, or actually a slight increase in the latter group.[71] Thus this remains an unsettled but extremely interesting area for further study. It is made particularly intriguing by the observations, pointed out earlier, concerning the obvious clinical forms of humoral hypertension, in which the sympathetic tonus, if not actually decreased, appears to be holding a "check rein" on the level of the blood pressure which is released by sympathetic blockade.

B. *Quantitative Aspects of Blood Pressure Response to Noxious Stimuli:* That the magnitude of change produced by emotional stimuli is frequently as marked as change produced by physical stimuli has not always been appreciated. Reiser et al. have demonstrated this fact clearly in their studies.[46] Recently, we have demonstrated that the magnitude of response of blood pressure in the hypertensive patient to the simple "emotional" stresses of intravenous injection of 10 ml. of normal saline, or of performing a mental exercise under pressure, frequently is equivalent to the effect of a standard cold pressor test, although the qualitative pattern, in terms of the

ratio between systolic and diastolic rise, may differ.[55] Moreover, the impact of psychologic forces may affect blood pressure chronically as well as acutely, and result in prolonged elevations lasting several days under controlled clinical observation.[56] These effects, therefore, are not merely minor or transient ones which play no important physiologic role, but are as potent as those which follow stimuli of nonpsychologic origin.

Peripherally, the physiologic changes which follow noxious psychologic stimuli include both vasoconstriction, with a decrease in renal blood flow and rise in filtration fraction, and tachycardia, with an increased cardiac output, as has been demonstrated by such work as that of Hickam et al. in normal individuals,[33] and Wolf and his co-workers in hypertensives.[76] Blomstrand and Löfgren have observed "anemization" of the renal cortex of cats after emotional stress by means of intravital staining with India ink.[6] Occasionally, increased peripheral vasoconstriction can be observed directly in the fundal arterioles in man,[45] and increased vasomotor activity in the conjunctival capillary bed following anxiety has been reported in both hypertensive and normotensive subjects.[37]

C. *Physiologic Patterns of the Blood Pressure Response; Their Relationship to Psychologic Affect and Other Factors:* One of the fascinating questions concerning the changes in blood pressure which follow noxious stimuli is why some individuals appear to react with vasoconstriction and others with increased cardiac output. Both responses would raise blood pressure, with the former primarily tending to affect diastolic pressure, and the latter, systolic pressure. Since hypertensive disease is an ailment in which the hallmark is increased peripheral resistance, it is the rise in diastolic blood pressure with which we are most concerned. An attractive possibility is that the difference in the response of different individuals depends upon the relative amounts of noradrenalin and adrenalin which are released into the circulation. It has been suggested by Funkenstein that a specific emotional response consisting of anger which is directed inward in the individual results in adrenalin elaboration, whereas when anger is directed towards an outside object and associated with activity, release of noradrenalin results. "Anger-in" appears to be an emotion equated with fear or anxiety, whereas "anger-out" involves aggressive, hostile behavior.[25] These inferences have been given some corroboration by work such as that of Elmadjian [21] and Cohen and Silverman [13] and their respective collaborators. Elmadjian has compared noradrenalin and adrenalin excretion among several groups of individuals in which clear differences presumably could be drawn between subjects with evidence of "aggressive and active" emotional states ("anger-out") and those with a "tense, anxious, but passive" display of emotion ("anger-in"). He reports a predominant increase in noradrenalin excretion in the former group, and an increase in adrenalin excretion in the latter. For instance, among a group of ice hockey players tested before and after a game, noradrenalin excretion increased markedly in the wingmen, who

are continually active and carrying the fight to the enemy. On the other hand, two players who were unable to play because of injuries, but who watched the entire game, showed a marked increase in adrenalin excretion. The goalie, who plays an extremely tense but passive role and skates very little, showed an increase in both noradrenalin and adrenalin, while the coach showed no change in excretion of either amine. Cohen and Silverman have demonstrated a difference in noradrenalin/adrenalin (NA/A) ratios physiologically by comparing "G" resistance in individuals following both structured interviews and contrived situations designed to produce "anger-in" or "anger-out." Since "G" resistance depends upon the degree of vasoconstriction elicited to prevent pooling of blood in the lower extremities, it was assumed that enhanced "G" resistance would indicate increased noradrenalin excretion. Thus the correlation between increased "G" resistance and the emotional state representing "anger-out," which these investigators observed in a small number of patients, was taken to support Funkenstein's hypothesis. Further confirmation was provided by their demonstration of higher NA/A ratios in the urine of several of these subjects following the test.

One difficulty with these conclusions arises in attempting to interpret accurately the emotion which the subject is experiencing. At best, the decision as to what constitutes "anger-in" or "anger-out" remains a subjective measure. Elmadjian's data would indicate, for instance, that the ice hockey goalie, although tense and anxious as he guards the net, is also aggressively angry, while the coach is a gentleman with the rare ability to remain supremely confident in his team's ability and detached from any aggressive feelings toward his opponents; to measure these attitudes as independent variables, however, is a formidable task. Similarly, while precontest data in a group of boxers showed high excretion values of adrenalin, a number of these contestants showed a fall in noradrenalin following their fights, and what is more aggressive and hostile than a boxing match? In addition, studies such as that of Bogdonoff and co-workers, employing contrived psychologic stimuli in which cardiac output changes were seemingly a function of intensity rather than quality of the emotional response,[7] and that of Imhoff et al., who have demonstrated the increasing systolic component of blood pressure response to stress with age,[36] should be emphasized as illustrating psychologic and somatic factors, other than the direction of anger, which influence cardiovascular responses.

As a further complication, although the predominant physiologic pattern in the individual subject may be the result of the specific emotion evoked by the stimulus, it could represent also a characteristic one for him which is usually activated regardless of the stress applied or the emotion evoked. As Funkenstein [25b] and Silverman et al.[13b] point out, the latter is apparently the case among different animal species, for Goodall has noted that the primary secretion in "aggressive" animals (cats and one lion) is nor-

adrenalin, while in "anxious, retreating" species (rabbit) adrenalin predominates.[27] Variation of pattern of response within a given individual, which Cohen and Silverman have noted in some instances, does not necessarily support the view that in man emotional affect rather than a characteristic catecholamine discharge determines the nature of the response. As we have indicated earlier in this review, additional pathways may be involved in the response of the blood pressure to noxious psychologic stimuli, and their relationship to the type of emotional reaction has not been studied.

The problem is not clarified when the hypertensive patient is studied, for, as demonstrated by Wolf et al.[76] and by van der Valk,[70] changes predominantly in either cardiac output or peripheral resistance may occur among different patients with hypertension, and even occasionally within the same patient. Brod and co-workers have indicated that both vasoconstriction and vasodilation occur in the hypertensive individual with the total change in peripheral resistance representing a summation of these factors.[8] Thomas et al. have demonstrated that individuals with family histories of high blood pressure tend to have a higher mean cardiac output, while those with a hereditary background of coronary artery disease have a lower output than do individuals with a history of neither ailment in their family.[68] Eich et al. have shown that younger, more labile hypertensives tend to have high resting cardiac outputs and normal peripheral resistance, while those with more fixed levels of pressure have normal outputs and increased peripheral resistances;[20] and Widinsky et al. provide evidence that young hypertensive subjects respond to muscular work and mental arithmetic with a further increase in cardiac output.[75] In our own current studies of blood pressure responses to a variety of psychologic and physical stimuli, both sex and age appear to play as significant a role as does the nature of the stimulus in determining the pattern of response in the hypertensive, with changes in the systolic pressure being more prominent in women and in older individuals.[55] Thus a specific tendency for the hypertensive subject, who does indeed tend to be aggressive and hostile in his emotional reactions, to react physiologically always with the "noradrenalin pattern" does not seem to be present.

At the present time, therefore, the question of what determines the specific pattern of the physiologic response remains an unsettled one. To draw broad inferences which attempt to explain development of chronic hypertension, or even the mechanisms of the acute changes in the clinical course of the hypertensive patient from the available data, seems to be rather premature.

D. *Technics for the Study of Psychophysiologic Responses:* A few comments are indicated concerning technics that have been employed in the various psychologic studies in hypertensive patients. There have been essentially two: (1) the retrospective analysis of emotional, situational and physical events, with an eye toward the establishment of temporal correlations; and (2) the structured interview, in which topics considered to be

particularly traumatic, as derived from prior personality study, are presented. Both methods have yielded much valuable information but, with both, subjective impressions are difficult to control, and neither lends itself to use in a predictive study. Grinker and his co-workers have discussed the problems of the "anxiety interview," pointing out, for example, that what is intended by the investigator to be stress-producing may often actually be reassuring.[29] Reiser has made an attempt in the direction of short-term predictive technics

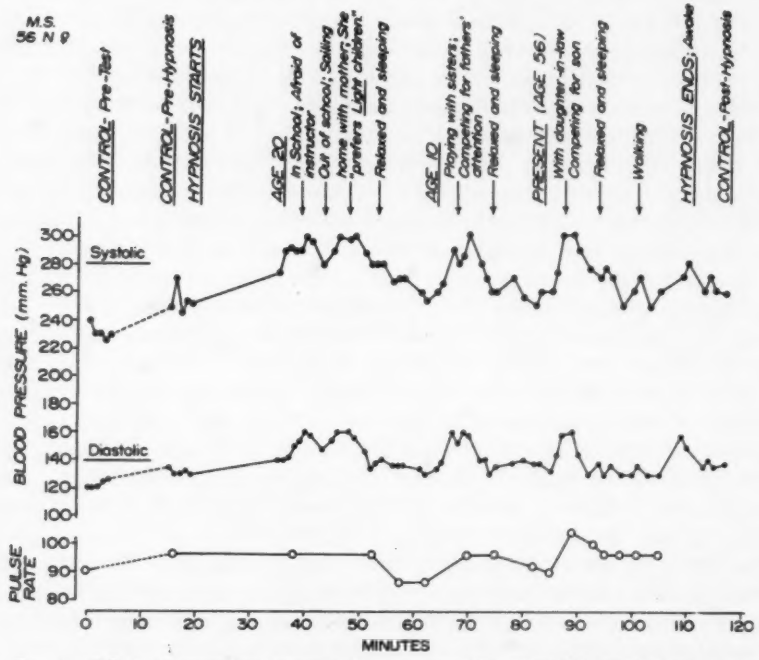


FIG. 1. Effect of regressive hypnosis in a woman with essential hypertension. At each age period, certain conflictual situations, involved with interpersonal relationships, are associated with marked spikes in blood pressure. In contrast, declines in blood pressure occur during periods of relaxation induced by suggestion. The hypnotic session itself was stressful, as indicated by the slight rise in base line blood pressures from pretest levels. (This study was performed in coöperation with Dr. Harold Krasilnek, Department of Psychiatry, Southwestern Medical School of the University of Texas.)

by acting as an observer who, from psychodynamic material obtained in control sessions with the patient's therapist, attempts to deduce subsequent developments in the clinical course of the patient.[45] This is a promising approach, but one which has limited applications. An observation we have made suggests a refinement of the "structured interview" technic. It involves the use of hypnosis, as is illustrated in figure 1. The patient was subjected to regressive hypnosis, and at each age level settled at a conflictual period which prior knowledge indicated contained considerable unresolved

resentment and hostility. Regression to these areas resulted in marked blood pressure elevation. Hypnotic suggestion which removed her from these situations resulted in decline of pressure.

Such studies, however, remain largely "post hoc" evaluations, while our need, as Mirsky has pointed out, is for the development of "propter hoc" technics.[41] In hypertension, this implies long-range longitudinal studies of populations, but the studies perhaps can be simplified and telescoped by the application of genetic knowledge and the use of physiologic and biochemical tests which might tend to pinpoint the potentially hypertensive population. Another unexploited approach is the use of conditioned reflex technics, a method which has been employed extensively in Russian research but has had limited employment in this country.[64]

2. Is There a Unique and Specific "Hypertensive Personality"?

Probably more has been written about the "hypertensive personality" than about any other psychosomatic feature of the disease. In common with most ailments with psychosomatic components, the hypothesis of the specific personality type has been entertained but has not been established. However, a picture of certain specific conflictual states or patterns of behavior in patients with hypertension has emerged. The subject has been reviewed by Moses, as part of his long-range study of psychotherapy in selected hypertensive patients, a study which will be discussed in detail further on in this paper.[43] Patients with hypertension appear to mobilize excessive and seemingly continuous anxiety and rage in response to deprivation of infantile dependent needs and threats to their security status. Frequently these reactions constitute their predominant affective manifestations towards the supportive figures in their environment—family, physician, etc. This affect is partially suppressed, either consciously or unconsciously, is not bound to neurotic symptoms, and is inadequately displaced into aggressive verbal or motor activity, lest by such activity their security status be threatened further. In brief, the hypertensive patients display an inordinate fear of loss of love and security, coupled with anger and hostility toward the people in their environment who do or could offer these dependency relationships, but who at the same time can thus dissolve them.

Fear and suppressed hostility are the prominent characteristics noted by the physician; the patients often appear sullen, suspicious, haughty and "smoldering," but, on the other hand, may be agreeable to the point of obsequiousness, seemingly to avoid offense. To the physician who treats the hypertensive individual the striking feature is the observation that a meaningful therapeutic relationship forms slowly and with considerable resistance, regardless of whether the patient's attitude is initially condescending or ingratiating. This feature contrasts with the individual with peptic ulcer, who similarly may initially fear and resist a dependent relationship, but does so for reasons concerned with *fear of being overwhelmed by his*

dependent needs, rather than the *fear of rejection* which seems to concern hypertensive patients.

In carefully controlled studies such as those of Saslow et al.[52] and Harris et al.,[32] the incidence of certain of these behavioral features in hypertensive or prehypertensive individuals is greater than in normals. Yet this is not to say that diagnostically the patient with hypertension shows a greater incidence of clinical psychoneurosis or psychosis. The argument that the lack of such an increased incidence of psychiatric disease mediates against the importance of emotional forces in hypertension is not a valid one, since what has been described is a behavior pattern and not a clinical psychiatric ailment. Indeed, since it has been pointed out that the anxiety is not effectively bound to phobic, hysterical or obsessive symptoms, one might postulate that the incidence of clinical psychiatric disease would actually be lower in the hypertensive than in the normal population, as in fact a few studies have suggested.[49, 3]

That these patterns of behavior are present in many normotensive individuals cannot be denied. What has been more impressive in our experience, however, is that few significantly hypertensive individuals are without at least some of these traits. Even patients with primary renal disease and hypertension, insofar as they have been investigated, may display the characteristic patterns of behavior.[5, 44] The situation may be akin to that which Engel has pointed out in ulcerative colitis,[22] namely, that the conflictual state is a necessary ingredient to the development of hypertensive vascular disease, but contributes to the production and progression of the disease only when other physiologic components are also present.

We can therefore summarize this section by pointing out that studies of hypertensive patients do not indicate a specific personality type, but rather the presence of certain specific patterns of behavior which are most obvious in interpersonal relationships. It is unlikely that these patterns play a primary etiologic role in the disease, but quite probable that, given a predisposition to vascular disease, they hasten its development and influence its progress. Further evidence for these latter statements follows.

3. Can Hypertensive Disease be Caused "Purely" by Emotional Stimuli?

A. *Clinical and Experimental Investigations:* As has been implied in the previous section, convincing evidence is lacking that chronic hypertensive vascular disease may develop *de novo* as the result of noxious psychologic stimuli. Since acute elevation of blood pressure regularly follows such stimuli, it has been assumed that their prolongation will lead to chronic elevation and subsequent organic pathology. However, with the exception of the studies in animals in the U. S. S. R. which have been reviewed by Simonson and Brozek,[64] experimental proof of this hypothesis has not been forthcoming.

Several reports of "spontaneous" clinical experiments are worthy of mention. Ruskin et al. observed that approximately 56% of a group of 180 survivors of the Texas City explosion displayed diastolic blood pressures of 95 mm. Hg or over from one to two weeks after the event.[51] Graham, studying a group of 695 men who had been exposed to long periods of combat in the desert during World War II, observed that 27% showed diastolic blood pressures of 100 mm. Hg or above for periods of from one to two months after return from prolonged campaigning (average of the entire group of 695, 154/90 mm. Hg).[28] Similar findings have been noted in Russian and Finnish combat troops in World War II.[26, 19] These observations are of considerable interest, but at most suggest only that prolonged exposure to severe stress, which is at least partially physical, may result in temporary elevations of blood pressure. The production of elevated levels of blood pressure in rats by means of audiogenic seizures, originally reported by Farris et al.[23] and later confirmed by Rothlin and co-workers,[50] would seem to represent an experimental model of what Ruskin and Graham have observed, but the bearing of these data on clinical hypertensive vascular disease is not clear. Similarly, the hypertensive vascular lesions reported by Selye in rats exposed to stress are primarily the result of extreme physical exhaustion.[52]

Russian investigators have approached this problem with Pavlovian conditioning, and we are indebted to Simonson and Brozek for their careful review of the status of Soviet research in this area.[64] Isolated reports of the production of transient and occasionally permanent hypertension in dogs have appeared, but the major efforts in the Soviet Union in recent years have been in monkeys. Spontaneous hypertension has been described in this species, and in a small number of monkeys permanent hypertension, with electrocardiographic and fundal changes, has developed incident to the production of experimental neuroses. In many respects, the disease described in these animals is identical with essential hypertension. These studies lend considerable support to the etiologic importance of the emotions to hypertensive vascular disease, but do not explain the relatively small incidence of the disease in the exposed animals, or the wide variance in severity.

In our own studies we have attacked this problem similarly by employing avoidance conditioning technics in cats[57] and rats.[4, 58] Although the methods we have used would seem productive of continuous anxiety for long periods of time, permanent hypertension or lesions of hypertensive vascular disease did not develop. On the other hand, in a group of rats subjected to a figure-of-eight ligature of one kidney and contralateral nephrectomy, hypertension appeared sooner (figure 2), and cardiac and renal lesions were more severe when the rats were subjected to a type of behavioral disturbance.[59]

There are two possible explanations of the failure regularly to produce hypertensive vascular disease *de novo* in animals, namely, that (1) the necessary specific emotions cannot be produced in the lower animal, and it

is of note in this regard that the positive results reported in the Russian literature are primarily in primates; or (2) the proper vascular predisposition, genetic or acquired, is not present. Our present state of knowledge does not offer us any ready answer to this question, but it is our opinion that the data do point toward the second of these alternatives.

B. *Genetic Predisposition and Its Relationship to Other Factors:* The presence of genetic factors in the development of hypertension seems well substantiated, and it is beyond the scope of this paper to discuss the evidence in any detail. The studies of Hamilton and his colleagues have done much

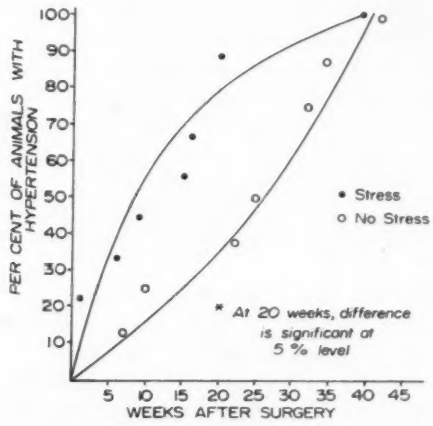


FIG. 2. Chart indicates the rate of development of hypertension following figure-of-eight tie of the right kidney and left nephrectomy in a group of rats which were stressed by noxious psychologic stimuli during a type of avoidance conditioning, as contrasted with a control group. All animals in both groups eventually became hypertensive, but the rate appears to be more rapid in the stressed animals, with the difference significant at 20 weeks.

to substantiate the importance of inherited traits in the development of hypertension, but at the same time have emphasized the interaction of environmental variables with the genetic predisposition.[31]

The environmental or acquired variables include not only the noxious psychologic stimuli, as we have discussed here, but also diet, physical stress, and diseases or conditions which may affect the vascular system or its reactivity. For instance, much evidence suggests that sodium may play an important role in hypertensive vascular disease. There is experimental evidence that the sodium content of arteries may be increased in hypertension,[69] that serum sodium [35, 1] and total body sodium are increased,[48] that the extracellular volume and body water are expanded,[67] that hypertensives handle salt loads differently than do normals,[15] and that low sodium diets or sodium depletion by diuretics is of therapeutic value.[74] Recently, Dahl and co-workers have presented data suggesting that individuals who nor-

mally take large amounts of salt with their food tend to have higher blood pressures.[16] The obvious question is whether sodium potentiates the genetic trait, and thus leads to the development of the hypertensive disease, or whether the genetic predisposition to hypertension manifests itself in some fundamental disturbance in the handling of salt. It is pertinent in this respect to note that Conn has observed that the incidence of hypertension in patients with Addison's disease receiving desoxycorticosterone acetate, and possibly the postoperative persistence of hypertension in primary aldosteronism, are related to the presence of a family history of hypertension,[14] while Hall and Hall have shown experimentally that continued stress with electric shock in rats receiving desoxycorticosterone acetate and salt produces a more severe hypertension than does desoxycorticosterone acetate alone.[30]

Further illustration of the combined effects of genetic and environmental factors is provided by the data which recently have been accumulated by Moser in the Bahamians.[38] It is now a rather well recognized fact that hypertension is more frequent in the Negro in the United States than in the white population.[38] Genetic differences, the increased psychologic stress experienced by the Negro in our society, and a greater incidence of primary renal disease in this group have all been invoked as possible causes. Moser reports the quite striking fact that, in the Bahamians, the incidence of hypertension rises to the point where, in age groups over 40, more than 50% of the population have diastolic blood pressures over 90 mm. Hg, which is considerably higher than the incidence in Negroes in this country. Coupled with this observation is the fact that the salt intake of the Bahamians is very high, since the sodium content of their water averages 100 to 200 mg. per 100 ml. Comparable data on the blood pressures of whites living in the area are not available in his studies, but we would hope would be forthcoming, for here we may be dealing with an epidemiologic experiment which might enable us to sift out the various component factors contributing to the disease. Similarly, comparisons of family histories of hypertension with the incidence of blood pressure elevation in groups of individuals divided on the basis of salt intake, determination of the incidence of hypertension following development of such acquired ailments as glomerulonephritis among individuals with and without a family history of hypertension, and the examination of the effects on blood pressure of noxious psychologic stimuli in individuals with and without a genetic predisposition all represent examples of the type of combined epidemiologic and physiologic studies necessary to evaluate further the proportionate role of the several factors involved. This problem has been emphasized recently by Neel, Francis and others.[35] It is of interest that, in Ruskin's study of 180 survivors of the Texas City explosion which we have mentioned previously, the Negroes in the group showed a 70% incidence of elevated blood pressure, as contrasted with 50% in the whites (chi square $= 4.1$; $p = .05$).* [51]

* Our calculation.

4. Is There Evidence of Aggravation of Preëxisting Hypertensive Vascular Disease by Emotional Stimuli?

Data are available which indicate that patients with hypertensive disease may undergo aggravation of their clinical course with appropriate emotional stress. Indeed, striking evidence is provided by Reiser et al. that malignant hypertension is usually precipitated in the patient with a previously benign course by a meaningful life situation which contains highly charged conflictual elements of a nature quite specific for the particular individual.[46] In our own experience, the temporal correlation of such events to malignant progression is perhaps the one factor most consistently present when an explanation for this transition is sought. Not only are the over-all aspects of malignant deterioration of the hypertensive patient influenced by noxious stimuli of psychogenic origin, but, as Chambers and Reiser have shown, specific areas such as the precipitation of cardiac decompensation may also be affected.[12] Evidence also has accumulated that emotional stress may be a precipitating factor in cerebral vascular accidents.[18]

If emotional stimuli play a significant role in the progression of hypertensive vascular disease, is this merely a question of the "quantity" of the stress, or do factors concerned with the specific physiologic reaction of the patient determine in whom the disease will progress and in whom it will pursue a relatively benign course? Again we are faced with the question of specificity of the emotional stimulus versus specificity of the physiologic reaction, a query to which a definitive answer is not available. Whether noxious stimuli affect cardiac output or peripheral resistance may influence prognosis, but, as has been discussed earlier in this review, both stressor and substrate are important in determining the predominant pathway.

Thus, it appears that emotional stimuli may precipitate a number of crises in the course of hypertensive vascular disease, and notably its progression into the malignant phase. That the presence or absence of such noxious stimuli is primarily responsible for the marked variations which the course of individual patients with benign essential hypertension may pursue is an attractive possibility, but by no means a proved fact. Much additional study of the relative roles of both the stress and the host factors is necessary before definitive conclusions can be formulated.

5. Is Psychotherapy Effective? Does it Cure?

Considerable evidence has been accumulated of the effectiveness of psychotherapy in the management of the hypertensive patient, even when it is administered unsuspectingly by an attentive physician during the course of his routine medical care. So potent are the effects of such a therapeutic doctor-patient relationship in ameliorating symptoms, levels of blood pressure, and indeed even physical signs of the disease, that they pose a formidable problem in evaluating the effects of even quite active hypotensive drugs.[60]

The enthusiasm of the investigator performing a drug assay we have shown to be a force which can be measured by appropriate technics of experimental control, and can exert a hypotensive effect often equal to or greater than the pharmacologic effect of a drug itself.[61, 62] In a series of 98 patients who were treated with no specific hypotensive drugs for an average of 21 months, Reiser and co-workers demonstrated over-all improvement in the majority of the group.[47] Diminution of symptoms occurred in 60 to 80%, blood pressure fell in 30 to 60%, and physical findings improved in 20 to 45%, with the percentage of improvement in each of these areas increasing with greater intensity and depth of psychotherapy. The psychotherapy in these patients was administered in most instances by nonpsychiatrists as part of the over-all medical management of the patient. Similar results have been reported by Weiss [73] and by Wolff and Wolf.[77]

There is a characteristic feature of the management of the hypertensive patient that seems to result in this ameliorative effect. This is the establishment of a doctor-patient relationship in which the patient is able to accept a dependent role, yet still feels secure and is unthreatened by fears of the dissolution of this relationship when his aggressive impulses are displayed.[63] Often the physician must play an essentially nonauthoritative role. Although it might appear that such an attitude on the part of the physician would be unsuitable in a disease in which considerable medication frequently must be administered, actually it seems to counteract the patient's hostile reaction to authority and his tendencies to act out by refusal to follow the prescribed regimen. In actual practice in our experience, a nonauthoritative attitude on the part of the physician often results in better coöperation in drug therapy and less "testing" of the relationship by the patient. Nor does this imply undue permissiveness; rather, it is typified, for instance, by refusal of the doctor to become angry and rejecting, or to voice predictions of doom, to a patient who, often seemingly in a quite provocative manner, has neglected his medication or some other aspect of his therapeutic program. In view of what has been pointed out earlier about the specific behavior patterns of the hypertensive patient, the rationale of this form of management is apparent.

Results from such management include only amelioration of the disease, or sometimes merely maintenance of the status quo and prevention of progression. Reversal of the malignant phase of the disease to a benign course has been demonstrated only in rare instances, in conjunction with the use of psychotherapeutic technics aimed at resolving conflicts revealed by psychodynamic study.[43, 46, 73] However, most of the so-called "spontaneous" remissions of malignant hypertension may well result from psychotherapeutic maneuvers, unplanned in a formal sense. Mere hospitalization, for instance, is a quite potent force, which may have powerful benefits.[60]

In these studies, claims for actual "cure" have not been made. It would seem reasonable, however, in view of the probable precipitating role of

emotional factors in the development of hypertensive vascular disease, that intensive psychoanalytic therapy might be curative, at least in terms of converting an actual hypertensive patient with irreversible pathologic changes back to a "potential" hypertensive. A long-range study attempting to validate this hypothesis was undertaken by Moses in 1948. His first report, in 1956, concerned itself with 10 patients, some of whom had been treated for as long as five years.[43] In this group were three individuals with malignant hypertensive disease, two with fixed hypertension, and five with labile hypertension. His results have been quite remarkable. Three of the "labiles" became normotensive, while the remaining two demonstrated no significant change but had been in therapy only briefly at the time of the report; the two "fixed" became "labiles"; two of the three "malignants" discontinued therapy very shortly after its institution, while the third converted to a benign "fixed" hypertension. Although Moses' results indicate the value of psychoanalytic therapy, particularly in the early "labile" hypertensive, the formidable problems concerned with the availability of psychoanalysis make it an impractical solution for the vast majority of the hypertensive population. More important is the fact that the demonstration by Moses provides additional evidence of the psychodynamic influences in hypertension. Furthermore, it offers both an explanation for the effectiveness of the doctor-patient relationship in the routine medical management of hypertensive patients and a rationale for the manipulation of this relationship.

To summarize, then, there is evidence that the proper and rational use of the doctor-patient relationship has a potent ameliorative effect in hypertensive vascular disease, and that, in selected patients with early labile hypertension, psychoanalysis may result in "cure."

Summary and Conclusions

The present status of our knowledge concerning the psychophysiologic aspects of hypertensive cardiovascular disease has been reviewed. It would appear that there is ample evidence that physiologic pathways exist by which emotions can be translated into blood pressure elevation. Such effects are undoubtedly responsible for many of the acute and even chronic rises in blood pressure seen in hypertensive individuals, and are probably among the factors causing aggravation of the disease. It seems unlikely, however, that psychogenic disturbances are ever solely responsible for the original development of hypertensive vascular disease, but, on the other hand, the evidence suggests that these influences are involved as contributing causes.

Understanding the precise mechanisms by which noxious psychologic stimuli may contribute to the etiology of hypertensive disease can make little real progress until basic physiologic mechanisms are unraveled further. On the other hand, revelation of basic physiologic mechanisms requires the continued instillation of knowledge derived from psychologic investigation.

In a disease such as hypertension, where psychodynamic influences are so intertwined in physiologic mechanisms, such parallel study is vital, whether the investigator be concerned with renal hemodynamics, evaluation of drugs, or analysis of personality.

Meanwhile, it would seem that supportive psychotherapy has something to offer in the management of hypertensive disease. This includes amelioration of symptoms, slowing of progression, avoidance of iatrogenic noxious stimuli, and adjustment of the patient's attitude to his environment and his disease. Psychotherapy in most instances should not be offered as a separate part of therapy; it is probably most effective when it becomes part of a supportive, nonthreatening doctor-patient relationship established, often without conscious plan, by the physician charged with the patient's over-all medical management. Our present understanding of the psychodynamic forces which result in the typical behavior patterns of hypertensive patients provides a rationale for the establishment of such a relationship. Moreover, knowledge of the impact of emotional variables should serve to illustrate to the physician that he does have some control of the situation, and should help him to manipulate the relationship as individual circumstances dictate. In certain instances, most typically the young individual with labile levels of blood pressure, more intensive psychotherapy is warranted, and, when available, such patients may derive considerable benefit by effective psychoanalysis. It is to be emphasized that none of these maneuvers obviates or interdicts the intelligent use of hypotensive medications. Rather, they may simplify the physician's task in employing these drugs when they are appropriate to the particular stage of the patient's disease.

Finally, we would point out that the psychophysiologic mechanisms involved in hypertensive disease are not magical manifestations. They are subject to investigation by the same scientific principles employed in other disciplines, and, when this is done properly, the observations should command the respect and attention of all clinicians and investigators—both the "psychiatrically oriented" and the "organically minded"—who are interested in advancing our basic understanding of hypertensive vascular disease. This is a multifaceted disease, requiring the technics of a number of disciplines and the integration of facts from different sources, if we are to achieve its ultimate understanding.

Acknowledgment

The author wishes to acknowledge his indebtedness to the late Eugene B. Ferris, M.D., who supplied the impetus to the development of many of the ideas expressed in this essay.

Summario in Interlingua

Es revistate le stato de nostre cognoscentias con respecto al aspectos psychophysiologic de hypertensive morbo cardiovascular. Il ha multe indicationes que circuitos physiologic existe per que emotiones pote esser traducite in elevationes del tension de sanguine e que iste circuitos functiona per medio de mechanismos tanto neurogene como etiam humoral. Tal effectos es indubitabilemente responsabile pro

multe occurrentias de acute e mesmo de chronic elevationes del tension de sanguine que es observate in subjectos hypertensive, e illos es probabilemente inter le factores que causa un aggravation del morbo. Tamen, le factos e observationes etiam suggere que multe variabiles—incluse etate, sexo, e le intensitate e le signification del evenimento psychologic—exerce un influentia super le natura qualitative e etiam quantitative del responsa pressori al stimulos nocive. Multe recerca—utilisante technicas psychologic si ben como physiologic—es ancora necessari pro clarificar le relative contributiones de iste variabiles. Il es pauco probabile que pertubationes psychogene es unquam exclusivemente responsabile pro le disveloppamento original de un hypertensive morbo vascular, sed il non pare possibile dubitar que iste influentias ha le rolo de causa contributori, como—per exemplo—quando illos interage con un genetic o acquirite predisposition vascular.

Le si-appellate "personalitate hypertensive" probabilemente non existe como distincte entitate clinic, sed il es certo ver que studios de patientes con hypertension ha demonstrate un modo particular del comportamento de illes in lor relationes interpersonal. Iste modo es characterisate per le timor de esser rejicite per personas in positiones cardinal e resulta particularmente in le incapacitate del patiente de gestionar impulsos aggressive. Le casos in que un intense psychotherapia es applicabile al hypertension per se es rar, sed si le medico presta attention a ille conflictos cardinal, ille pote utilisar le psychotherapia como tractamento supportative que contribue significativemente al melioration del regime medical in general. Il pare ben establite que tanto le melioration del symptomas como etiam le stabilisation del tension de sanguine—e forsan mesmo un retardo del progresso del condition—pote resultar in parte ab un tal therapia supportative.

Es signalate in conclusion que mechanismos psychophysiologic ha un rolo importante in omne phases de morbo hypertensive e que le investigatores—sin reguardo a si lor interesse es primarimente therapeutic o hemodynamic o etiologic—debe prender iste paramentro in consideration.

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ABO BLOOD GROUPS IN THE ACCELERATED FORM OF HYPERTENSION * †

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THE accelerated ("malignant") form of hypertension is characterized by the presence of widespread necrotizing arteriolitis and proliferative endarteritis. When it appears after the prior development of primary (essential) hypertension, it has been regarded by some investigators as a phase representing an increased intensity of the hypertensive process.

A number of clinical observations [1, 2] support the view that factors other than tempo play at least a part. The present study deals with the frequencies of ABO blood groups.

CLINICAL MATERIAL

The ABO blood groups were determined in white and Negro men and women with the accelerated form of hypertension, there being 45 subjects in each series. All patients (from the wards and clinics of the Columbia-Presbyterian Medical Center) gave a history of at least four years of an established diastolic hypertension, and had recently developed proteinuria, progressive renal damage and retinopathy, usually with papilledema. Their diagnosis was established and primary renal disease was excluded by the history and clinical course, by pyelography in the majority, and, in most instances, by the finding of necrotizing arteriolitis in a renal biopsy obtained at the time of sympathectomy or at autopsy.

RESULTS

The results are summarized in table 1. Only one Negro woman (whose father was Irish) had a group A blood, a reduced frequency approximating four times the standard error when related to the expected incidence in Negro women. The remaining variations were of no statistical significance in a group of this size. For comparison, of 2,259 patients typed for transfusion in the Presbyterian Hospital over a six-month interval, 1,011 (45%) had group O blood; 865 (38%), group A; 286 (13%), group B; and 97 (4%), group AB. When these were subdivided into various racial and

* Received for publication December 8, 1959.

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† Aided by grants from the Union County, N. J., Heart Association, and the Albert H. and Jessie D. Wiggin Foundation.

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TABLE 1

The Frequency of ABO Blood Groups in the Accelerated Form of Hypertension

Blood Group	Men		Women	
	White	Negro	White	Negro
O	23	26	27	30
A	17	10	13	1
B	4	5	4	12
AB	1	4	1	2

ethnic groups, 27% of 370 Negroes and 43% of 364 Jews had group A blood, whereas the percentages in the total white population and in those of European derivation lay between these extremes.

COMMENTS

The present study discloses a significant decrease in the frequency of group A blood in Negro women with the accelerated form of hypertension when compared to white women and Negro or white men. This difference does not appear to be explainable on the basis of ethnic variations. Although control data were obtained from the same geographic setting, it would be of interest to have confirmation through larger series and through studies in other localities; a larger series might reveal differences in the frequency of other blood groups. As with the previous study of body type from this clinic, these results are as yet of no diagnostic significance, although group A blood has been encountered in this clinic in several Negro women with the accelerated form secondary to renal disease.

The accelerated form of hypertension is more common in men than in women, and there is a higher incidence in the Negro.[2] The present study provides additional evidence of a host factor which cannot be environmental, and which contributes to the susceptibility of Negro women to this disorder.

SUMMARY

A significant decrease in the frequency of group A blood in Negro women with the accelerated form of hypertension adds to the evidence that host factors play at least a part in the susceptibility to this disorder.

ACKNOWLEDGMENT

We are indebted to Dr. John Scudder and Richard H. Osborne for data from the Presbyterian Hospital Blood Bank.

SUMMARIO IN INTERLINGUA

Le gruppos de sanguine ABO esseva determinate in patientes con le forma accelerate de hypertension. Esseva includite subjectos de ambe sexos e de racia

blanc e negre. In cata serie il habeva 45 subjectos, e le diagnose esseva confirmate per datos clinic e pathologic. Solmente un femina negre habeva sanguine del gruppo A, durante que le distribution del gruppos de sanguine esseva normal in patientes de racia blanc e in masculos negre. Iste observation provide un prova additional pro le rolo de un factor in le hospite, non de character ambiental, que contribue al susceptibilitate de feminas negre pro iste disordine.

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METABOLIC PROTECTION AND RECONDITIONING OF THE HEART MUSCLE THROUGH HABITUAL PHYSICAL EXERCISE*†

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In the medical literature of the Soviet Union it is customary to begin scientific articles with a reference to I. P. Pavlov's *Collected Works,* regardless of whether the subject bears any close relationship to them or not. At the outset of the following discussion, however, no reasons of etiquette are needed to give credit to the great Russian physiologist, whose doctor's thesis (1883)[1] was based on his early fundamental studies concerning the cardiac sympathetic nerve, including its "trophic" significance, which was to be disregarded in the West for many decades.

It is one of the psychologic paradoxes of our time that modern American cardiology, with its stupendous progressiveness in other respects, has until quite recently imperturbably avoided consideration of neurogenic biochemical pathogenic mechanisms in the origin of functional and degenerative diseases of the heart. With the advent of improved and simplified methods of catecholamine assay in blood and tissues, however, this traditional aloofness has suddenly given way to a widespread and intensive preoccupation with the biochemical and cardiotoxic effects of the sympathetic system and of its neurohormones, norepinephrine and epinephrine.

An international symposium on the subject, *The Catecholamines in Cardiovascular Pathology,* held in 1959 at the University of Vermont,[2] provided eloquent testimony to the potentially highly cardiotoxic effects exerted by both norepinephrine and epinephrine on the metabolism, function and structure of the myocardium.

(A) Pathogenic and Protective Neurovegetative Influences on the Heart

Under normal circumstances, sympathetic and vagal neurosecretory activities are purposefully integrated in cardiovascular homeostatic functional patterns under the equilibrating guidance of the central nervous system.[3, 4] However, a variety of extraordinary conditions in the central nervous sys-

* Received for publication December 30, 1959.

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† The writer's own investigations upon which the viewpoints of this article are based were supported by research grants from the Rockefeller Foundation, The John and Mary R. Markle Foundation, the U. S. Public Health Service (National Heart Institute), the American Medical Association, the Vermont Heart Association, the U. S. Department of State (Fulbright Commission in Vienna), and the Universitätsbund Innsbruck, Austria.

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tem as well as in the periphery are capable of aggravating the potentially oxygen-wasting, efficiency-impairing, hypoxiating and necrotizing properties of the adrenosympathogenic catecholamines [5, 6] to acutely or insidiously harmful and even fatal degrees. The most important and most common of these catecholamine-"toxifying" conditions are: (a) exaggerated discharge of catecholamines by the cardiac sympathetic nerve terminals and/or by the adrenal medulla (e.g., due to abnormal central nervous stimulation or excess catecholamine formation in the periphery, as in cases of pheochromocytoma, thiamine deficiency,[7] etc.); (b) potentiation of catecholamine-induced oxygen wastage by the thyroid hormone [6]; (c) provocation of catecholamine-induced myocardial hypoxia by coronary atherosclerosis, arterial hypertension and ventricular hypertrophy [5]; (d) potentiation of necrotizing catecholamine effects by adrenal corticoids; [8-11] (e) deficiency of counterregulatory sympatho-inhibitory or vagal cholinergic mechanisms, permitting an undue adrenergic preponderance in myocardial metabolism.[5, 12]

As far as the latter mechanisms are concerned, it is known that the vagus preserves cardiac oxygen and increases myocardial efficiency by slowing the heart rate, and possibly also by as yet poorly understood favorable cholinergic influences on ventricular inotropic behavior and oxygen economy.[5, 13] However, no vagal fibers reach the ventricles, and the existence of a genuine negative inotropic action of the vagus and of acetylcholine on ventricular dynamics is still controversial, even though the ventricular tissue contains relatively large quantities of acetylcholine.[5] Some negative inotropic effects, observed in intact animals and human beings,[13] may be attributable to reflectory stimulation of recently discovered cardiac sympatho-inhibitory centers in the hypothalamus.[14, 101]

(B) Exercise Habits and Neurovegetative Status of the Heart

One of the most impressive examples of powerful cholinergic and/or sympatho-inhibitory regulatory effectiveness is the so-called "athlete's heart." It was formerly dreaded because of its often abnormally, though not pathologically, large size ("regulatory" dilatation [15]), but is now recognized as highly efficient and resistant to stress.[15-18] Its characteristically slow rate, rapid deceleration after exercise, and prolonged isometric period of the left ventricle at rest have heretofore been interpreted as the expression of an overdeveloped cholinergic vagal tone.[15, 16, 19, 20, 21] In the light of the above-mentioned newer investigations,[14] however, the possible participation of an augmented sympatho-inhibitory central nervous activity must also be taken into consideration.

In any event, the prevalence of effective antiadrenergic neurovegetative regulatory mechanisms with all of their cardiodynamic advantages in highly trained individuals, and especially in endurance athletes,[15, 16] suggested the

possibility that the opposite—namely, a deficiency of these mechanisms—might be involved in the origin of various functional and degenerative cardiac anomalies. This applies in particular to pathologic conditions with a more or less conspicuous sympathogenic adrenergic background, such as angina pectoris,[5, 6, 22, 23] neurogenic hypertension,[24] myocardial degeneration and ventricular failure.[5, 12] These are characterized by typically catecholamine-induced manifestations: hypoxic cardiac pain, accelerated heart rate, arrhythmias, reduced energetic efficiency,[25, 26] subendocardial necrotic and fibrotic foci (resembling those elicited by catecholamine infusions,[5, 27a, 28, 29] or by catecholamine discharges from pheochromocytomas [27b]), and metabolic abnormalities (loss of glycogen and high energy phosphates), which are likewise analogous to the cardiac metabolic effects of experimental catecholamine intoxication.[5]

Significantly, all of these signs and symptoms can be mitigated or abolished by specific antiadrenergic procedures:[5, 6, 12] catecholamine-reducing sympathectomy, ganglionic blockade and rauwolfia drugs, catecholamine-depotentiating thyrostatic therapy and adrenalectomy, and catecholamine-antagonizing vagal and/or sympatho-inhibitory stimulation (carotid sinus compression, morphine). The action of digitalis, although not strictly cholinergic, resembles that of vagal stimulation in that it diminishes the heart rate and improves myocardial oxygen economy and efficiency. Finally, there is mounting evidence that the increasingly advocated therapeutic utilization of various types of physical exercise in overtly cardiac patients (see below) may also be based, in part, on the restoration of an adequate vagal cholinergic and/or sympatho-inhibitory tone.

In view of the above enumerated direct and indirect indications of a potentially pathogenic adrenergic preponderance in functional and degenerative diseases of the heart, on the one hand, and of the apparently advantageous role of highly developed vagal and/or sympatho-inhibitory mechanisms in physically trained individuals on the other, 360 healthy men with widely varying exercise habits (ages 17 to 50) were tested at rest regarding heart rate and length of isometric period of the left ventricle ("chronodynogram")[30] (figure 1). The latter parameter serves as a sensitive indicator of neurovegetative influences, in that a shortening of the isometric period (or "tension period," TP) occurs under sympathetic adrenergic action, a lengthening under cholinergic and/or sympatho-inhibitory influence.[13]

Our test subjects were divided into four groups: (1) American and European sportsmen, hard-working mountain peasants and soldiers of High Mountain Units of the Austrian Army (subgroup I+: competitive endurance athletes); (2) men engaged in regular but lighter sports, routine military training, nonmotorized farm laborers in the plains, patrols of the Austrian State Police; (3) men with only irregular and scanty sports activities, and physically not strenuous occupations (mechanics, factory

workers, etc.), walking not more than three miles per day; (4) nearly completely sedentary individuals.

The average results showed clearly a proportionate relationship between the degree of habitual physical exercise, on the one hand, and the neuro-vegetative status of the heart on the other: with increasing exercise habits, there was a linear decrease of sympathetic tone (diminution of heart rate and lengthening of the isometric period TP) (figures 2, 3), and vice versa.

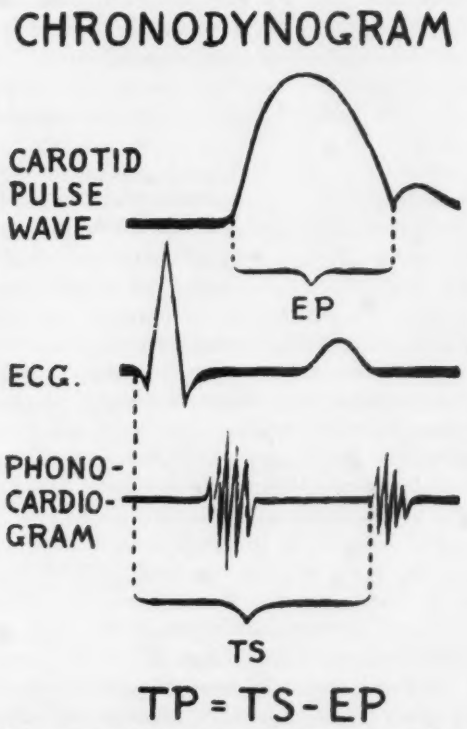


FIG. 1. Measurement of isometric period of the left ventricle "TP" (method of Blumberger).[13]

The high vagal and/or sympatho-inhibitory tone of sportsmen and other people engaging in heavy exercise does not seem to be merely a preëxisting constitutional trait. It largely disappears after cessation of regular exercising,[16, 18, 31, 32] and it can be demonstrably acquired by training periods of only a few weeks or months.[16, 21, 33–36] This was also confirmed by our own observations on 20 students before and after 6 to 12 weeks of strenuous sports activities (figure 4). Changes in the opposite direction were found to develop during prolonged bed-rest (figure 5), and to persist for weeks after resumption of normally active living.[37]

Interestingly, smoking habits did not noticeably affect the basic neurovegetative cardiac status of our test subjects, despite the immediate and distinct but evanescent (about 30 minutes per cigarette) adrenergic reaction elicited by the process of cigarette smoking.[38]

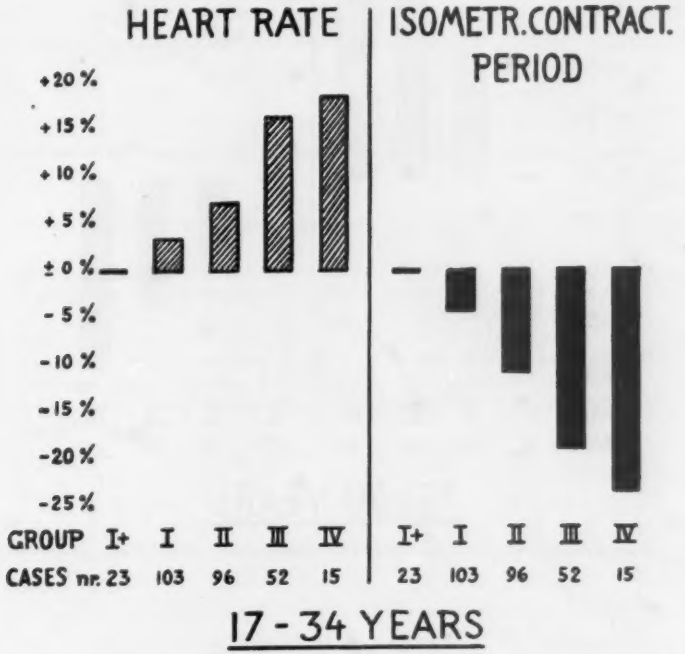


FIG. 2. Percentagewise increase of average resting heart rate, and decrease of length of average resting isometric period of the left ventricle (TP, see figure 1), in proportion to decreasing exercise habits, indicate shift from cholinergic and/or sympatho-inhibitory to sympathetic adrenergic preponderance with decreasing exercise habits.[30]

(C) Cardiac Pathogenic Implications of Sympathetic Overactivity Due to Lack of Exercise

The pathogenic implications of an exaggerated cardiac sympathetic tone, resulting from lack of physical exercise, seem to be consistent with the results of extensive statistical studies,[39–45, 68] according to which the morbidity and mortality from degenerative heart disease, especially myocardial infarction, are significantly lower and occur later among physically active than among sedentary individuals.

Some other investigators do not recognize a major significance of exercise habits in the occurrence of coronary heart disease. In a group of men, 25 to 40 years of age, with clinical coronary disease, Russek and Zohman [46] found severe emotional strain of occupational origin to be the most important

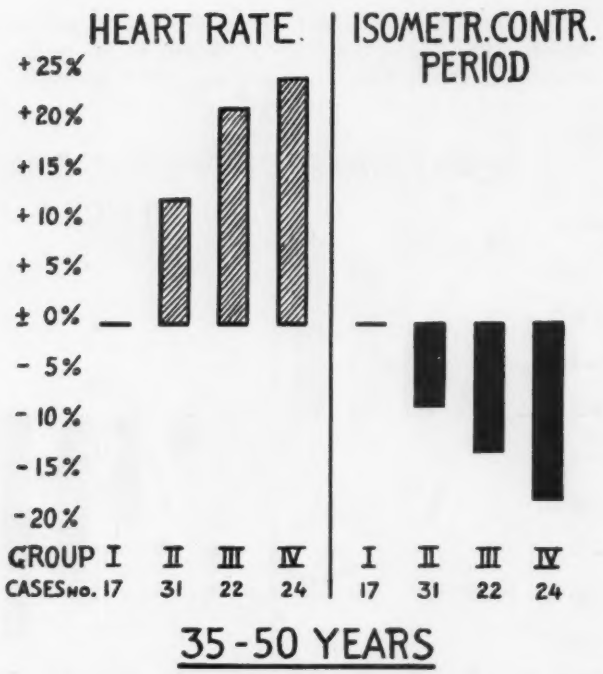


FIG. 3. Same principle as figure 2, manifested in older age category.[30]

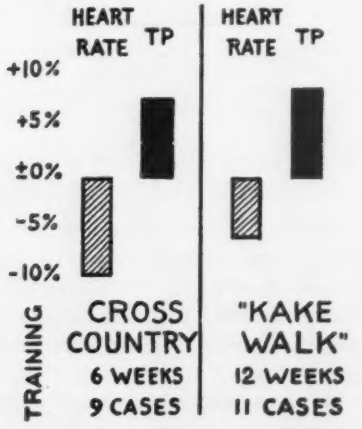


FIG. 4. Percentagewise decrease of average resting heart rate and lengthening of average isometric period (TP) indicate shift toward vagal cholinergic and/or sympatho-inhibitory preponderance in 20 students as a result of temporary physical training.[30]

common pathogenic denominator, regardless of exercise habits. However, with regard to this type of urban patients, one may assume that prolonged emotional overexcitation of the sympathetic nervous system [47-50] might have been powerful enough to wipe out whatever cardiac metabolic benefits their probably limited exercising would otherwise have provided.[47] A similar reasoning may apply to the investigations of Friedman and Rosenman [51] and Stamler,[52] whose observations concerning the role of exercise in the

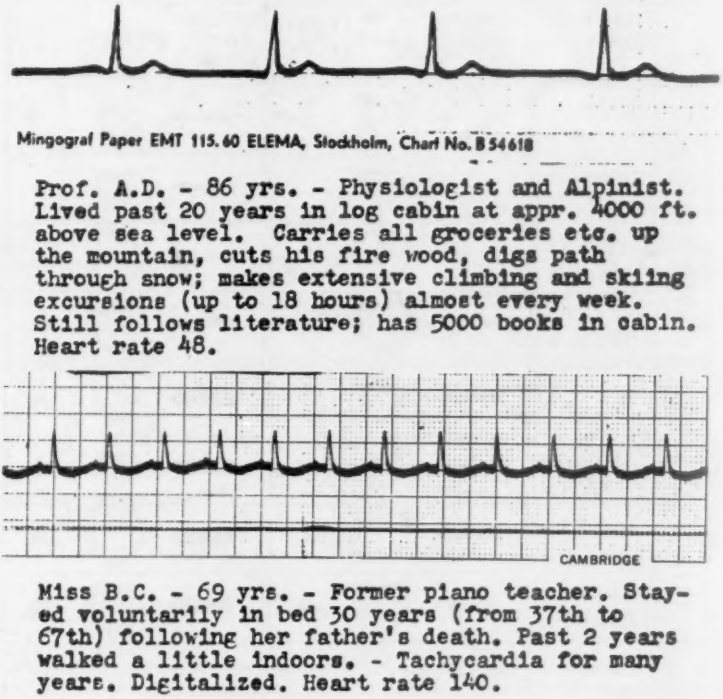


FIG. 5. Electrocardiograms of two extreme cases: one of habitual vigorous exercise until age 86, the other of voluntary bed-rest for 30 years.[30]

origin of coronary heart disease and atherosclerosis were inconclusive. Ancel Keys,[53, 54] in emphasizing chiefly the importance of dietary fat in the development of coronary atherosclerosis, also expresses a skeptical view regarding the significance of occupational exercise.

Longevity studies in relation to exercise habits revealed that cardiovascular morbidity did not differ significantly between former college sportsmen (most of whom had long ago ceased to engage in regular sports) and other comparable individuals.[55, 56] These findings are probably less informative than those obtained by Karvonen et al.[42] in Finland, according to

which continuation of regular sports activities into later life increased its duration by an average of seven years.

In evaluating the presumable heart-protecting role of habitual exercise, one must distinguish between neurovegetative influences on the heart muscle itself and those on the coronary arteries.[40] It appears significant that

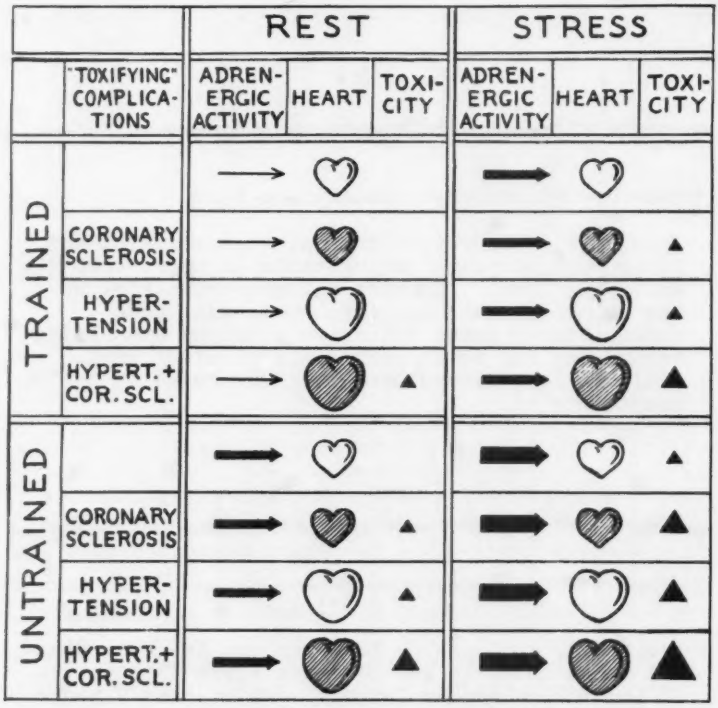


FIG. 6. Schematic representation of the degree of potential cardiac toxicity (hypoxia, structural damage, efficiency impairment) resulting from sympathetic adrenergic catecholamine activity in normal and in pathologically predisposed hearts (with reduced oxygen supply due to coronary sclerosis and/or increased oxygen requirement due to arterial hypertension and cardiac hypertrophy). Stressful situations intensify adrenergic activity. In untrained individuals, sympathetic adrenergic preponderance exists even at rest. Its further accentuation by stress constitutes an additional threat to myocardial function and structure in the presence of aggravating "toxifying" circumstances, such as coronary sclerosis and/or arterial hypertension and cardiac hypertrophy.

Schumann [57] found the catecholamine-induced myocardial metabolic changes after acute exercising less pronounced in trained than in untrained animals.

From daily experience it is well known that a healthy myocardium in a generally normal internal environment is vigorously stimulated but only very rarely injured [58] by the acute temporary influx of neurogenic and adrenal medullary catecholamines during the process of exercising as

such.[20, 59] On the other hand, the maintenance of a more or less permanently elevated sympathetic tone, as caused by lack of exercise and/or by prolonged emotional tensions, seems to create in the heart muscle an unfavorable, metabolically hazardous situation, especially when it coincides with vulnerability-increasing hypoxiating coronary atherosclerosis, arterial hypertension and ventricular hypertrophy (figure 6). The great importance of the time element in "toxifying" even small extra amounts of catecholamines (norepinephrine) has been clearly demonstrated by Szakács and Mehlman.[27a]

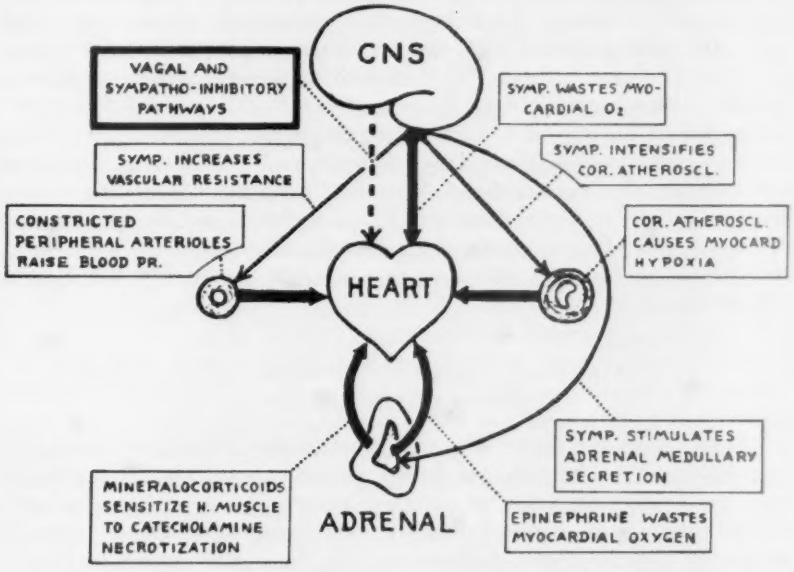


FIG. 7. The heart muscle under concentric neurohormonal biochemical metabolic and hemodynamic attack. In the trained individual, the highly active vagal and sympatho-inhibitory mechanisms (heavily dotted line) exert an, at least partially, protective influence. In the untrained individual, these protective, counterregulatory mechanisms are deficient ("loafer's heart"). (From Kraus, H., and Raab, W.: Diseases from lack of exercise; courtesy Charles C Thomas, Springfield, Illinois, 1960.)

Hyperplasia of the arterial intima and accelerated, intensified intimal deposition of lipids under the influence of injected epinephrine and norepinephrine have been observed in the aorta and large vessels of cholesterol-fed animals.[60] Similar reactions were provoked by enforced exercise in the coronary arteries.[61] By contrast, an antiatherogenic influence of prolonged exercise has been described regarding the aorta and coronary arteries of rabbits [62, 63, 103] and birds.[64, 65] No such effect was seen in rabbits in another study.[66] In human beings, some evidence has been obtained, suggesting a lesser degree of aortic atherogenesis in athletes than in more sedentary individuals.[67] Morris and Crawford [40] emphasize that, in their large sta-

tistical material (3,800 autopsies), no relationship could be established between degrees of occupational physical activity and the incidence of coronary atherosclerosis, whereas a definite relation existed between the incidence of "ischemic myocardial fibrosis" and lack of exercise.

Thus it appears that a protective neurovegetative influence of habitual vigorous exercise is more clearly established regarding the myocardium than regarding the coronary arteries. Over-all cardiac morbidity from coronary disease should be substantially reduced by a lessened vulnerability of the myocardium, as provided by exercise-induced cholinergic and/or sympatho-inhibitory mechanisms. This factor may account for the reported lower and later incidence of cardiac disease and deaths in physically active as compared with sedentary people,[39-45, 68] despite an about equal distribution of coronary atheromatous lesions in both groups.[40] Morris and Crawford [40] interpret their findings as a "further suggestion that ischaemic heart disease is not a simple function of coronary artery disease." This conclusion agrees well with our often expressed view [5, 6, 12] that "ischaemia"—i.e., disproportion between oxygen supply and consumption—can be caused by specific metabolic oxygen-wasting catecholamine action alone, as well as by a narrowing of the coronary bed, and, of course, to a maximal degree, by a combination of both factors.

(D) Cardiac Reconditioning and Rehabilitation Through Physical Exercise

A review of the above discussed observations permits the assumption that vigorous physical exercise habits (together with dietary precautions and, if possible, avoidance of excessive emotional stresses) contribute to the maintenance of myocardial health by preventing an undue sympatho-adrenergic overactivity in the heart muscle, the crucial feature of "loafer's heart." [5, 69] (The Russian translators of this writer's monograph on "The Adrenergic-Cholinergic Control of Cardiac Metabolism and Function" [5] preferred to introduce the scientifically more dignified term, "detrenirovannoye syerdce"—"detrained heart." [70])

No definite explanation is yet available of the mechanism by which exercise habits modify the neurovegetative resting tonus of the heart. Changes in cerebral cortical and hypothalamic stimulus formation, and an involvement of conditioned reflex processes appear to be the most likely possibilities in view of the dominating role played by the central nervous system in cardiac functional regulation.[4, 14, 71] Combined electrocardiographic and electroencephalographic investigations of Letunov [100] have provided suggestive evidence that the training-induced shift of the central stimulus formation toward the vagal and sympatho-inhibitory side is due to functional alterations in the cerebral cortex. The sympathetic stimulations connected with emotional excitement, on the other hand, being chiefly of hypothalamic

origin, do not produce similar long-range beneficial effects on the neurovegetative cardiac equilibrium at rest.

Acceptance of this working hypothesis poses the question as to whether practical steps can be taken to make it clinically useful.

In view of the now widely appreciated fact that reasonably intensive occupational and sportive physical activities do not constitute any significant danger for the primarily normal heart muscle,[15, 16, 20, 59, 72, 73] the cultivation of endurance sports and strenuous games among unquestionably healthy young individuals is to be encouraged for somatic as well as psychologic reasons, however, with avoidance of "overtraining," particularly in the very young,[21, 74] whose cardiac sympathetic tone is high from the beginning and, therefore, subject to potentially harmful exaggerations.[21]

Endurance sports (running, swimming, cycling, cross-country skiing, etc.) are more likely to develop a high cardiac cholinergic and/or sympathoinhibitory tone than are mere strength and skill sports (wrestling, weightlifting, judo and the like[15, 32]). It is also important to remember that the neurovegetative gains made during a prolonged training period are apt to be largely lost within months or even weeks after discontinuation of physical activity.[16, 18, 31] Thus, in order to maintain a permanently adequate neurovegetative equilibrium in heart metabolism, one has to earn it day by day and year by year, as earlier generations have done and as is still being done in less pampered populations of our time. In agreement with a statement made by Mellerowicz,[16] we feel that our Western so-called "normal" hearts are in reality pathetic artifacts, insidiously degenerating products of supercivilized soft living, and much less "normal" in terms of the original species *homo sapiens* than those of our ancestors and sturdier contemporaries elsewhere, especially in those areas of the world which we condescendingly call "underdeveloped." Future extensive epidemiologic studies, simultaneously taking into account dietary and socio-economic conditions, should provide more positive information on this point.

With advancing years and with the gradual development of catecholamine-"toxifying" factors as listed in section (A), the impact of acutely exercise-induced influxes of catecholamines into the heart muscle, particularly in the "detrained" or "loafer's" heart, becomes more and more detrimental, causing anginal pain, arrhythmias, necrotic and fibrotic lesions, "pseudo infarctions"[104] and, ultimately, congestive heart failure and death (figure 6). The further advanced the complicating factors, such as coronary atherosclerosis, hypertension, and hormonal or nutritional abnormalities, the more necessary will it be to exert the utmost caution in attempts to recondition the heart through graded exercise practices. Hearts with primarily valvular and other anatomic lesions but with an essentially intact myocardium may be quite fit[75] and stand up remarkably well under great physical strain.[76] Those with coronary sclerosis and arterial hypertension, on the other hand, are likely to be thrown into serious difficulties under the

influence of stresses, including acute exaggerated exercise (= onrushing adrenergic catecholamines [4, 22, 77]), if these are superimposed upon an already overactive cardiac adrenergic resting tone (figure 6).

Work tolerance testing is therefore desirable before exposure of middle-aged and elderly, latent or overt cardiacs to the possible hazards of an increasingly vigorous systematic exercise training. Various such tests have been devised,[78-82] but the results are often misleading, due to differences in psychologic motivation and other uncontrolled variables. The profound influence of changing climatic factors on subclinically and clinically diseased hearts has been studied at rest,[83] but needs to be evaluated also in connection with exercise. The usually disregarded additional risk inherent in the variations of atmospheric temperature and humidity as stress-producing factors ought to be taken into consideration when training programs are being planned for individuals of the above-named type.

Despite such existing uncertainties and limitations, the outdated policy of immobilizing each recognized or suspected cardiac patient has been replaced in recent years by a much more rational and courageous attitude on the part of the medical profession and the lay public alike. This is largely due to steadily increasing reports concerning favorable results obtained when the calculated risk was taken to apply systematic exercise therapy to patients who, in the past, would have been treated as hopeless invalids.[84, 92]

At the XIIth Congress of Sports Medicine in Moscow in 1958, not less than eight reports from various parts of the Soviet Union were presented, dealing with satisfactory results of long-range exercise therapy in more than 3000 cardiac patients, for the most part convalescents from myocardial infarctions. In such conditions, the improved development of collaterals under the influence of exercise [93, 94] may constitute another favorable element.

Even more important than the rehabilitation of already manifestly diseased hearts is the timely reconditioning of those which, having not yet displayed any distinct signs of deterioration, are nevertheless headed for serious trouble. Successful attempts in this respect have been undertaken on a limited scale by Cureton,[35, 96] Arbeit et al.[97] and others;[98] but, by contrast to other countries (especially West Germany, Switzerland, Austria and the Soviet Union), no organized reconditioning programs for larger groups of sedentary individuals have yet been developed in the United States. Health consciousness here is still largely overshadowed by "disease consciousness" as the prevalent attitude.

In and near Ohlstadt, a small village of the Bavarian Alps, more than 10,000 middle-aged and elderly sedentary men have been exposed to intensive year-round outdoor reconditioning practices during the last decade, owing to the initiative of Dr. P. Beckmann.[99] Because of the economic advantages inherent in the resulting reduction of absenteeism, medical expenses and early invalidism, the financial support of this and 12 similar, more recently developed organizations has been taken over by large Western

German insurance companies and industries (Siemens-Halske and Brown-Boveri Electrical Works, Mannesmann Steel Works). The right of the individual insured worker or employee, up to age 65, to be sent for from three to six weeks to one of the rural reconditioning centers has been established by federal law. Candidates are selected on the grounds of the following general criteria: (1) stabilization of the blood pressure on an elevated level; (2) circulatory abnormalities in heart, brain and limbs; (3) functional abnormalities of the heart; (4) functional abnormalities of the intestinal tract; (5) nervous exhaustion, insomnia and abnormal fatigue. Last year approximately 15,000 persons passed through such reconditioning courses, which consist of a medically supervised schedule of graded, noncompetitive outdoor sports, calisthenics, hiking, mountain climbing, swimming, etc., alternating with discussions and lectures, and avoiding the usual forms of "entertainment." At termination of the courses, instructions are given for continued home exercises.

In the Soviet Union, reconditioning programs of a similar nature for workers are being carried out on an infinitely larger scale in thousands of so-called "koororts" (from the German, *Kurort,* cure place) along the coast of the Black Sea, in the Caucasus Mountains, etc., and in the "night sanatoria" of the industrial plants. Claims have been made that heart disease in the U.S.S.R. is declining, but no specific data seem to be available at this time.

Whatever detailed statistics may reveal, it is astonishing and disquieting that the United States of America, although leading in the field of degenerative cardiac morbidity and mortality, lags far behind other, less afflicted nations in prophylactic initiative and planning. A great deal of pioneer work has been done in this country in the field of rehabilitation of the sick. However, an estimated $2,468,340,000 of earnings are lost here per year from heart disease.[102] It is to be anticipated that the proverbial "ounce of prevention" would prove to be more profitable for employees and employers alike.

Certain scenically attractive and climatically favorable areas in this country, especially the mountainous sections of the North, which offer all-year sports opportunities, appear to be ideally suited and ought not remain unutilized for the creation of mass reconditioning centers under the rigid supervision of competent medical staffs. Such centers would serve not only as an essential feature of public health maintenance, but also as a prerequisite for the expanded study of basic and applied reconditioning problems.

Summary

Lack of habitual exercise, an outstanding characteristic of present-day Western civilization, produces a statistically demonstrable sympathetic-adrenergic preponderance in the neurovegetative regulation of cardiac dynamics at rest ("loafer's heart" or "detrained heart"), in contrast to the

well known vagotonic and/or sympatho-inhibitory features of "athlete's heart." These shifts in the neurovegetative equilibrium are reversible by physical training and by prolonged lack of exercise, respectively.

Although a moderate degree of adrenergic over-activity in itself may not injure an otherwise healthy heart muscle, the potentially cardiotoxic metabolic properties of the adrenergic catecholamines (oxygen wastage, impairment of energetic efficiency, production of local hypoxia and necrotization) are greatly intensified if they coincide with such common vulnerability-increasing conditions as coronary sclerosis, arterial hypertension, cardiac hypertrophy, and certain hormonal and vitamin derangements.

Statistical and experimental observations suggest that inactivity-induced adrenergic preponderance contributes significantly to the high cardiac morbidity and mortality in overcivilized Western nations, even though the statistical picture is somewhat blurred by the common coincidence with atherogenic dietary factors (fat, cholesterol) and with overwhelmingly sympathostimulatory prolonged socio-economic and emotional stresses—factors which are also often prevalent in physically active individuals.

Smoking habits do not affect the resting neurovegetative state of the heart in between the temporarily sympathostimulatory individual acts of cigarette smoking.

No single, potentially pathogenic factor by itself can be made fully responsible for causing functional and degenerative heart diseases. However, various combinations of individually subthreshold but mutually aggravating mechanisms are prone to bring on catastrophe, either acutely or insidiously.

Systematic physical training under proper supervision is to be encouraged, even in the aging, since it is capable of removing at least one of the presumably major contributory elements in the pathogenesis of functional and degenerative heart disease. Successful mass reconditioning programs for this purpose are being carried out on a large scale in Central Europe and in the Soviet Union. The United States is leading in degenerative cardiac morbidity but lagging far behind in prophylactic vision and initiative. Since this country has given birth to the concept of preventive medicine, and since it possesses the material means to keep it alive and active, it has also the obligation to do so where it is most needed.

SUMMARIO IN INTERLINGUA

Manco de exercitio habitual—un characteristica prominente del civilisation occidental de nostre dies—produce un statisticamente notabile preponderantia sympathico-adrenergic in le regulation del dynamica cardiac in stato de reposo ("corde del face-nihil" o "corde dis-trainate"), per contrasto con le ben-cognoscite characteristicas vagotonic o sympatho-inhibiente del "corde de athleta." Iste deviationes in le equilibrio neurovegetative es revertibile per trainamento physic de un latere e per le prolongate manco de exercitio del altere.

Ben que un moderate grado de activitate adrenergic per se non debe vitiar un myocardio que es alteremente normal, il pare que le potentialmente cardiotoxic proprietates del catecholaminas adrenergic (guastation de oxygeno, perturbation del effi-

cacia energic, production local de hypoxia e necrotisation) es grandemente intensificate quando illos coincide con conditiones apte a augmentar le vulnerabilitate, como per exemplo sclerosis coronari, hypertension arterial, hypertrophia cardiac, e certe dysfunctiones hormonal e vitaminic.

Observationes statistic e experimental suggere que le preponderantia adrenergic inducite per inactivitate contribue significativemente al alte cifras de morbiditate e mortalitate cardiac in le hypercivilisate nationes del Occidente, sed il es ver, le situation es obfuscate un pauco ab le puncto de vista statistic per le frequente coincidentia de iste factor con atherogenic factores dietari (grassia, cholesterol) e con le effecto prolongate de stresses sympatho-stimulante a base socio-economic, le quales—evidentemente—se trova etiam in subjectos qui es physicamente active.

Le habitude del fumar non affice le condition neurovegetative del corde in stato de reposo. Le stimulation sympathic que es associate con le acto individual de fumar un cigaretta es un phenomeno temporari.

Il non es possibile signalar un sole specific factor de pathogenicitate potential que per se poterea esser reguardate como responsabile in toto pro le causation de morbos cardiac functional e degeneratori. Tamen, varie combinationes de factores individualmente subliminal sed mutualmente aggravatori ha le potentialitate de effectuar un resultato catastrophic, sia acute o sia insidiose.

Un programma systematic de trainamento physic sub directivas experte debe esser incoragiate mesmo in subjectos de etate avantiate, proque illo es capace a eliminar al minus un del apparentemente major elementos contributori in le pathogenese de morbo cardiac functional e degeneratori. Programmas de reconditionamento in massa es executate a bon successo in grande dimensiones in Europa Central e in le Union Sovietic. Le Statos Unite es in le vanguarda con respecto al incidentia de morbiditate cardiac degeneratori e in le retroguarda con respecto a vision e initiativa prophylactic. Viste que nostre pais ha disveloppate le idea del medicina preventive e viste que illo possede le medios material pro vitalisar e activar lo, illo ha etiam le obligation de facer lo ubicunque le desiderato es urgente.

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SIMPLIFIED PULMONARY PHYSIOLOGY FOR OFFICE PRACTICE *

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Introduction

The modern clinical approach to a patient should take into consideration not only the pathologic and etiologic aspects of his disorder but also his functional impairment and potentialities.

Accurate functional evaluation of the several components of respiration has been possible in the research environment for several years, and methodology is continually being improved. For the most part, this has been out of reach of the average practicing clinician and his patient. A complete evaluation of pulmonary function includes studies of all four of its basic components: ventilation or the bellows action of the lungs, distribution and mixing of the inspired air, perfusion or pulmonary blood flow, and diffusion or alveolar capillary respiration.[1]

Warring [2] has stated that the majority of pulmonary patients can be adequately evaluated by tests of ventilation alone. Our personal observation would lead us to extend this statement to say that over 90% of pulmonary patients can be adequately evaluated in this manner. Fortunately, tests of ventilation are also the simplest to perform. Several attempts have been made to develop equipment to enable the clinician to test ventilatory function with reasonable accuracy and simple technics. In each instance there has been some disadvantage. The ideal equipment for general use should combine low cost, simplicity of use, ease of maintenance and sterilization, compactness, and accuracy.

The Warring-Siemsen Ventube [3] and the McKesson-Scott vitalometer seemed to fill these criteria, and were selected for a clinical evaluation of accuracy.

Technic

On 200 consecutive referrals (representing 177 patients) to the Pulmonary Physiology Laboratory † each patient was tested both by the standard methods and by the simplified investigative procedure to be described.

* Received for publication November 24, 1959.

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TABLE 1

Clinical Diagnosis

1. Asthma	28
2. Bronchiectasis	25
3. Emphysema	22
4. Spontaneous pneumothorax	17
5. Solitary pulmonary nodule	15
6. Cardiovascular diseases	11
7. Chronic bronchitis	10
8. Diaphragmatic hernia	10
9. Pulmonary neoplasm	8
10. Pulmonary fibrosis	7
11. Pulmonary tuberculosis	6
12. Mediastinal diseases	6
13. Empyema	4
14. Fungus diseases	4
15. Pleural fibrosis	3
16. Sarcoidosis	2
17. Atelectasis	2
18. Other diagnoses	16

Note—29 patients had multiple diagnosis.

Tests were performed on 177 patients, several of whom were tested on more than one occasion. The patients ranged in age from eight to 54 years, with a mean age of 31. There were 154 males and 23 females. A remarkable cross-section of pulmonary disease was seen (table 1).

The standard investigation of ventilatory function is performed in the Pulmonary Physiology Laboratory of this hospital using the following



FIG. 1. McKesson-Scott vitalometer.

procedures and equipment. Total vital capacity (VC) and timed vitalometry (1- and 3-second) are performed on the Gaensler-Collins timed vitalometer.[4] Resting minute ventilation, oxygen consumption, maximum breathing capacity (MBC) and spirographic tracing, from which lung compartment values can be calculated, are performed on the 9 L. Collins



FIG. 2. Warring-Siemsen Ventube.

respirometer. In addition, the maximum expiratory flow rate (MEFR)[5] and maximum midexpiratory flow rate (MMEFR)[6] are calculated from the same spirographic tracing. The walking minute ventilation is performed utilizing the 50 L. Douglas bag and mask apparatus and a low pressure gas meter for volume measurement. In addition, the ventilatory equivalent for oxygen and the dyspnea index (DI) of Warring [2] are calculated.

In contrast to this somewhat complex laboratory investigation, the simplified technic being evaluated employed only the McKesson-Scott vitalo-

meter and the Warring-Siemsen Ventube (figures 1 and 2). The total vital capacity was determined on the former, and the maximum breathing capacity and walking minute ventilation on the latter. The dyspnea index was calculated from these data, as in the standard procedures.

The standard and experimental procedures were performed consecutively during the same laboratory appointment by separate technicians, and the results were recorded separately. One of the authors (R.B.S.) made the

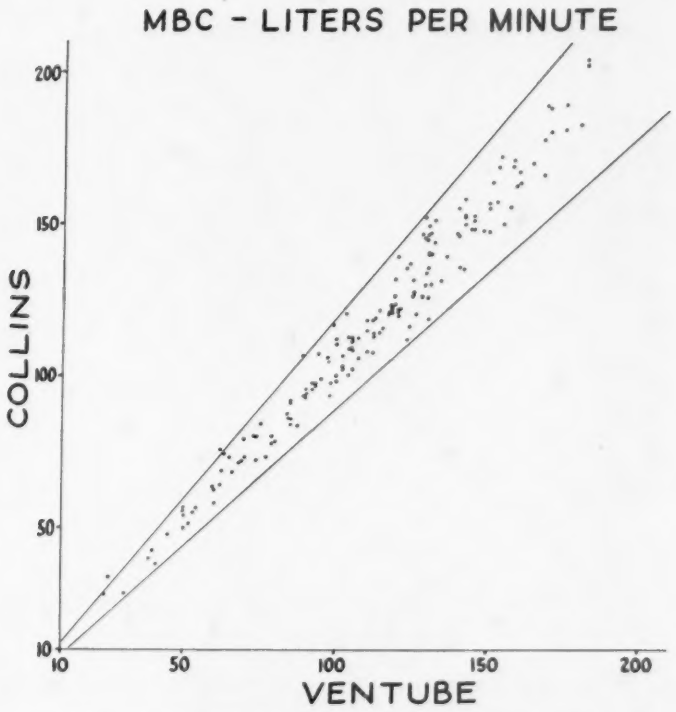


FIG. 3. Correlation of results obtained comparing standard and simplified methods of investigation for maximum breathing capacity.

clinical interpretation of the standard data, and the other (J.E.R) interpreted the simplified technic. The results of a careful chest fluoroscopy performed to observe rib and diaphragmatic motility and evidence of air trapping were available to both authors.

The maximum breathing capacity and the vital capacity were performed in both methods of investigation until the variation between efforts was minimized. Repeatability within 5% for the maximum breathing capacity and 3% for the total vital capacity was required. Since walking minute

ventilation does not require maximal effort, it was performed only once by each method.

Interpretation of the results of the maximum breathing capacity and the total vital capacity was based upon a comparison of the recorded results with the predicted normal values of Baldwin, Cournand and Richards.[7] Arbitrarily, values above 80% of the predicted volume were considered to

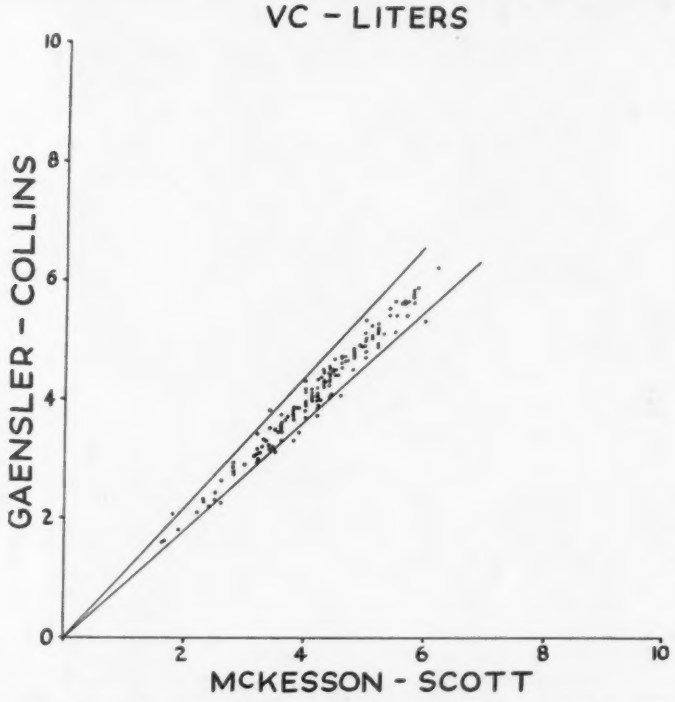


FIG. 4. Correlation of results obtained comparing standard and simplified methods of investigation for vital capacity.

be normal; those which were 60 to 79% were interpreted as demonstrating mild impairment; 40 to 59% indicated moderate impairment; and severe impairment existed when values were below 40%.

The Dyspnea Index was calculated as follows:

$$\frac{\text{Walking Minute Ventilation (liters per minute)}}{\text{Maximum Breathing Capacity (liters per minute)}} \times 100 = \text{Dyspnea Index}$$

Normal respiratory reserve was considered to be present when the dyspnea index was less than 25%. An index of 25 to 34% indicated mild impairment; 35 to 44%, moderate impairment; and a value of over 45%, severe loss of respiratory reserve.

Results

The correlation of the mathematical results obtained comparing the standard and the simplified methods is shown on the scattergrams (figures 3, 4 and 5). In each scattergram, 95% of the cases fall within the band contained by the two oblique lines. The variation between results by the two methods of testing was not significantly greater than the allowed difference in repeated tests on the same equipment (5% for maximum breath-

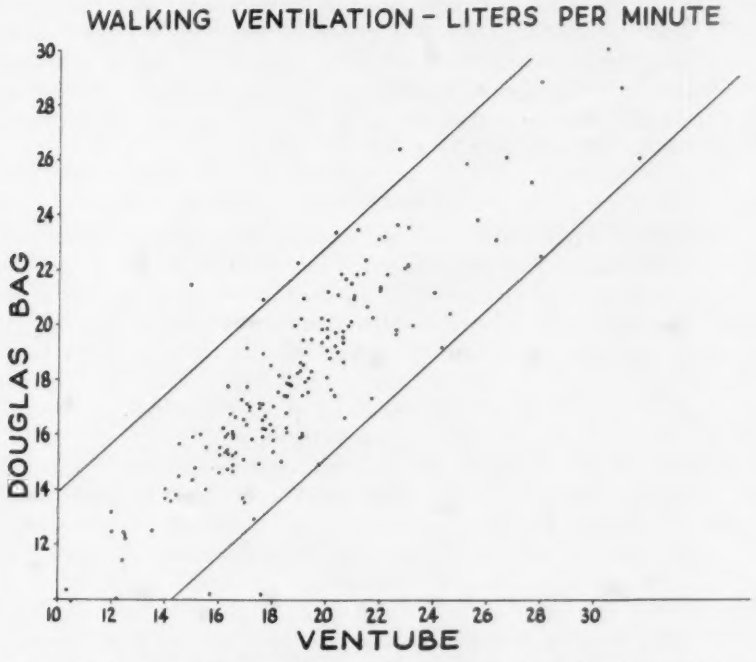


Fig. 5. Correlation of results obtained comparing standard and simplified methods of investigation for walking minute ventilation.

ing capacity and 3% for total vital capacity). Walking minute ventilation varied somewhat more, perhaps because the nature of the test makes repetition for reduction of error impractical.

Of greater significance than the mathematical correlation was the agreement experienced in the clinical interpretation comparing the two methods. No attempt was made to find the answers for more than three questions: What type of ventilatory insufficiency was present? What degree of impairment was present? What respiratory reserve was present as expressed by the dyspnea index? There was complete agreement between the two methods as to whether ventilatory insufficiency, either obstructive or re-

strictive in type, existed. In obstructive disorders, differences in the estimate of severity were noted in 11 tests. However, this was never more than one category difference (i.e., mild versus moderate, or moderate versus severe). In restrictive disorders, there was a difference in the estimate of severity in eight tests—again, never more than one category. It should be noted that individuals who were misclassified by the simplified method relative to the standard method were not necessarily the individuals with the greatest mathematical difference between the two methods. It was not only the function of the difference between the values but also the function of how near the values were to the arbitrary points on the scale used to separate the degrees of severity. When the dyspnea index was considered, there was complete agreement in 186 tests. Of the remaining 14 tests, only one test disagreed by more than one category (i.e., moderate impairment of reserve versus normal reserve).

Discussion

Ventilatory abnormalities are the most frequent cause of respiratory distress in chronic pulmonary disease. Thus, tests of ventilation are likely to be the most productive clinically. In the interpretation of tests of ventilation, the answers to three clinical questions are of primary interest: Does the patient have an impairment of ventilation? If so, what is the type of impairment? Can its severity and clinical significance be accurately quantitated? If this can be done, one can evaluate objectively the functional progress of the disease and the response to therapy.

Impairment of ventilation is classified into three types: obstructive, restrictive and combined. Obstructive insufficiency refers to conditions like asthma, emphysema, bronchial tumor or foreign body, inspissated secretions, and others in which there is a narrowing of the bronchial passages. This narrowing causes an increase in resistance to air flow. Logically, then, it is measured by any technic which relates volume change to time. Decreasing intrathoracic pressure during inspiration causes a general expansion of the bronchial passages, with resultant decrease in air flow resistance. In expiration, the opposite is true.

Many tests for obstructive ventilatory insufficiency are aimed at measuring time volume relationship on single expiratory efforts. The timed vital capacity, measured by the technic of Gaensler,[4] is widely accepted as a method of measuring single expiratory flow rate. The result is expressed as the percentage of the total vital capacity expelled in a given unit of time (one and three seconds in this laboratory). The method is simple and accurate, and has well established standards of normal. The Gaensler-Collins respirometer, however, is relatively expensive, nonportable, and seldom seen in the average clinician's office. Since the spirographic tracing recorded by the Collins respirometer is plotted against time, the same measurements can be calculated from this tracing. In addition, from the spirographic

tracing one can calculate the flow rate by the method of Cander and Comroe [5] (maximum expiratory flow rate), or by the method of Leuallen and Fowler [6] (maximum midexpiratory flow rate). Although the technic is simple and has well established standards of normal, the equipment is even more expensive and cumbersome. Attempts have been made to design simple instruments to measure flow rate. Wang and Shipley [8] combined the simple McKesson-Scott vitalometer with a portable time recording device, making possible the measurement of total and timed vital capacities, as well as maximum expiratory flow rate. A commercial modification of this principle is now available as the McKesson Vitalor. Goldsmith and Young [9] developed the Puffmeter, which utilizes a capacitance transducer polarized unit as a recording device. Unfortunately, these instruments are restricted to measurements of single breath flow rates.

Snider and his associates have recently reported "a simple semiquantitative bedside test for airway obstruction." [10] They tested the ability of a patient to blow out a match held six inches from the open mouth. While this test gave an indication of moderate or greater obstructive insufficiency, it could not differentiate this from severe restrictive disorders. It was suggested by the authors solely as a screening procedure.

The volume-time relationship of respiration can also be measured by a multiple breath technic, the maximum breathing capacity (MBC). This is the most valuable of the tests of ventilation, because it measures the functional ability of the total respiratory apparatus, including patency of the airways, elasticity of the lung neuromuscular forces, and coördination. These individual factors are usually easily differentiated by clinical and fluoroscopic examination. The maximum breathing capacity is most commonly measured on the Collins respirometer, the practical limitations of which have already been mentioned. The Warring-Siemsen Ventube utilizes the venturi principle to measure volume of air flow. Its accuracy in measuring the maximum breathing capacity has already been established.[3] The instrument approaches our ideal, combining low cost, simplicity of use, ease of maintenance and sterilization, compactness and accuracy.

Restrictive insufficiency refers to those conditions causing reduction in total number of functioning alveoli. Examples are: resection of lung tissue, pneumonia or atelectasis, pleural effusion or fibrosis, and parenchymal fibrosis. A time-honored method of reflecting restriction is measurement of the total vital capacity. Here, measurement of volume alone is important. Although it is usually measured by the Collins or Gaensler-Collins respirometer, such complicated equipment is unnecessary. Accurate, simplified instruments for this measurement have long been available and in general use—for example, the McKesson-Scott vitalometer.

Combined ventilatory insufficiency includes both obstructive and restrictive components, and is present in such disorders as emphysema with pulmonary fibrosis, and pulmonary edema.

The respiratory reserve can be thought of as the potential breathing ability of the patient over and above that called for by a specific degree of exercise. It can be expressed by relating the ventilation required to perform a standard exercise (walking 180 feet per minute) to the maximum breathing capacity. We have referred to this relationship as the dyspnea index. The walking ventilation is usually measured by collecting the expired air during the performance of the exercise in a Douglas bag fitted with face mask and unidirectional valves. The volume collected is then measured on a low resistance gas meter.[1] Equally accurate results can be obtained using the Warring-Siemsen Ventube. Reduction in reserve is clinically significant in that it correlates closely with the degree of dyspnea.[2]

Summary

The standard methods of investigation utilized in pulmonary physiology laboratories will reveal the data necessary for a complete clinical evaluation of respiratory function, but are not usually available to the practicing physician. Previous attempts to develop simplified equipment have been only partially successful, in that they have been limited in their scope of testing.

We have shown, in 200 consecutive cases, that the information necessary for an accurate clinical evaluation of ventilatory function can be obtained using only the Warring-Siemsen Ventube and McKesson-Scott vitalometer. These instruments are inexpensive, their combined published list price being $125.00. They are small enough to fit into a desk drawer. They can be accurately used by unskilled personnel after only moments of instruction and practice. Sterilization requires only immersion of the mouthpiece in alcohol. Maintenance rarely extends beyond cleaning. The entire test series can be accomplished in approximately 15 minutes.

Utilizing the dynamic maximum breathing capacity as a reflection of obstructive disorders, the vital capacity as a measure of restriction, and the walking ventilation to estimate reserve, we can answer three basic questions: Does an impairment to ventilation exist? What is its type, and severity? What is its clinical significance in relation to dyspnea? With the Warring-Siemsen Ventube and McKesson-Scott vitalometer, it has been possible to demonstrate a high degree of clinical accuracy, and to evaluate objectively the functional progress of the disease and the response to therapy.

Acknowledgment

The authors wish to thank the Department of Biometrics, USAF School of Aviation Medicine, USAF Aerospace Medical Center (ATC), Brooks Air Force Base, Texas, for the statistical analyses of the results obtained in this study. In particular, we are indebted to Dr. M. Brian Danford and Mr. Richard C. McNee.

Summario in Interlingua

Un del plus negligite areas del practica medical in nostre dies es le evalutation functional del banal patiente pulmonar. Ben que le laboratorios de physiologia pul-

monar es capace a effectuar un complete evalutation physiologic, lor servicios es rarmente disponibile al practico general. Le essayo de provider al clinico un equipamento appropriate a su uso ha essite facite repetitemente in le passato, sed o le equipamento non esseva vermente adaptabile al requirimentos del sala de consulta private o le gamma del tests effectuabile per medio de illo esseva troppo restringite. Le forma de equipamento que merita esser designate como ideal deberea combinar basse costos, simplicitate del uso, facilitate de mantenentia e de sterilisation, compactessa, e accuratia. Le Ventube de Warring-Siemsen e le vitalometro de McKesson-Scott pareva satisfacer iste criterios e esseva seligite pro un evalutation clinic.

Al occasion de 200 consecutive referimentos al laboratorio de physiologia pulmonar (representante un total de 177 patientes), le requirite tests esseva effectuate (*1*) secundo le technica standard del laboratorio de physiologia e (*2*) secundo un simplificate technica pro salas de consulta con le uso del duo supra-mentionate apparatos. Le morbos pulmonar representate in le gruppo constitueva un collection typic. Le resultatos esseva registrate e interpretate separatemente con le objectivo de trovar responsas a tres questiones fundamental: Existe il in le patiente un vitiation del ventilation? Que es su typo e grado de severitate? Que es su signification clinic in relation al dyspnea? Esseva obtenite un correlation frappante del interpretation clinic del stato functional del patiente secundo le prime del methodos con illos secundo le altere.

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PROBABLE HEPATIC ALLERGY TO CHLORPROMAZINE AND DELIBERATE DESENSITIZATION *

By Leo Waitzkin, M.D., *Brockton, Massachusetts*

This report issues from studies concerning the pathogenesis of hepatic dysfunction due to chlorpromazine, the prophylactic and therapeutic influence thereon of synthetic adrenocortical hormones, and trials of deliberate desensitization.

All of the patients studied had been hospitalized for neuropsychiatric illnesses, were in good physical health, and had no debilitating disease. Chlorpromazine was administered to them orally.

The same battery of liver function tests was employed throughout the studies. It was composed of thymol turbidity, zinc turbidity, cephalin flocculation,[a] bromsulfalein retention,[b] serum glutamic-oxalacetic transaminase [c] and usually serum glutamic-pyruvic transaminase,[d] serum alkaline phosphatase,[e] total serum bilirubin [f] and prompt, direct-reacting bilirubin.[g] After the studies were well under way, a modified Malloy-Evelyn method was substituted for the determination of total serum bilirubin [h] and one-minute direct bilirubin.[i] Serum cholesterol,[j] cholesterol esters,[k] serum albumin and globulin were determined occasionally. Liver biopsies were examined by Dr. H. E. MacMahon, Department of Pathology, Tufts University School of Medicine.

Charted as:

a. CF: Normal, negative or 1 plus in 48 hrs.
b. BSP: Normal, $< 4\%$ in 45 min.
c. SGO-T } : Normal, 4 to 40 units.
d. SGP-T }
e. APh: Normal, 1.5 to 4 Bodansky units.
f. SB: Normal, to 1.2 mg./100 ml. total.
g. DB.
h. TSB: Normal, 0.3 to 1.5 mg./100 ml.
i. 1'DB: Normal, 0.06 to 0.25 mg./100 ml.
j. Chol.: Normal, 140 to 250 mg./100 ml.
k. Esters: Normal, 50 to 65% cholesterol.

Probable Allergic Nature of the Basic Mechanism Underlying Hepatic Dysfunction Due to Chlorpromazine

Allergy is defined as "any specifically acquired alteration in the capacity of living tissue to react. This alteration in capacity to react results from exposure to an exciting agent and is manifest on reëxposure to the same or

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to an immunologically related agent." [1] The exciting agent is an antigen, and the specifically acquired alteration may be interpreted as the formation of antibody.

Criteria to be fulfilled before a process is regarded as allergic should include:

1. Immunizing event.
2. Latent period.
3. Accelerated reproduction of reaction upon reëxposure to a small challenging dose of the drug.
4. Specificity.
5. Demonstration of acquired antibody.
6. Desensitization.

Immunizing Event and Latent Period

Chlorpromazine was administered daily for at least one month to 68 patients who had not previously received the drug.[2] Dosage schedules ranged from 75 to 1,200 mg. daily, with a median of 461 mg.

Table 1

Time of Onset of Hepatic Dysfunction in 31 Patients Ingesting Chlorpromazine Daily for One Month

Days after Beginning CPZ	1–3	4	5–7	8–14	15–21	22–27
Number of patients	0	2	7	13	7	2

Prior to treatment, 50 patients had completely normal liver function tests. During the month of drug administration, 31 of these 50 developed asymptomatic hepatic dysfunction. Bromsulfalein retention was increased most frequently, serum transaminase less often, and serum alkaline phosphatase occasionally. Between initial internal contact with chlorpromazine and onset of hepatic dysfunction there was a latent period varying from four to 27 days (table 1).

The data suggest that, with daily administration of chlorpromazine, hepatic dysfunction will probably have appeared in practically all susceptible individuals within the first month. This is in accord with the fact that overt jaundice due to chlorpromazine has first been noted approximately one to five weeks after the initiation of drug therapy.[8, 10, 22]

Reproduction of Reaction Upon Reëxposure to Chlorpromazine

A separate group of 16 patients ingested chlorpromazine daily for periods ranging from three to 29 days before it was discontinued for sundry reasons (table 2). In 13 of the patients the drug was stopped promptly upon the discovery of icteric or symptomatic anicteric hepatic dysfunction. In the

TABLE 2

Episodes of Accelerated Hepatic Dysfunction Provoked by Reëxposures to Chlorpromazine

Case	RI	CPZ Exposures, Mg. Daily	Days After Initial CPZ Dose in Each New Reëxposure																						
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	17	19	20	21	22	25	28	31	38
1		*Initial Exposure*																							
36 yrs.	3wks.	a. CPZ 25, one dose. Prednisone 150, 6 days	LB. N	N	N	N																				
	1 wk.	b. CPZ 25, one dose.	SGP-T 92	185	208	136			115	110	72		76					N								
	3 wks.	c. CPZ 25, one dose. Prednisone 150, 6 days	LB. N	N																						
	1 wk.	d. CPZ 25, one dose	SGP-T N	79		60			N																	
	1 wk.	e. CPZ 25 daily. To 600 daily in 1 month			SGP-T 56						LB. N							LB. N					LB. N		LB. N	LB. N
2		*Initial Exposure*																								
32 yrs.	13 mos.	a. CPZ 5 daily, increasing to 30 daily in 1 mo. Prednisone 150 concurrent, 35 days. Pre-CPZ: BSP 11.5%; SGP-T 66		BSP 16 SGP-T 98			12.5 88		11.5 107					13 106									11 154 APh 4			
	4 mos.	b. CPZ 25, one dose	BSP 16 SGP-T N	17 82				8 73							N N											
	19 days	c. CPZ 25, one dose. Prednisone 150, 6 days	BSP 10 SGP-T N	7 44	8.5 N							8.5 70					N 79				7 60			6 66	
	12 wks.	d. CPZ 25, one dose	BSP 14 SGP-T 57	11 79					8 49																	
	1 wk.	e. CPZ 25 daily. To 600 daily in 6 weeks. Pre-CPZ: BSP 8%; SGP-T 49	BSP 8 SGP-T 46	8 48	8.5 42	9 44			9 53			9 46									6 N				
3		*Initial Exposure*																								
59 yrs.	6 wks.	a. CPZ 25, one dose. Prednisone 150, 6 days	LB. N	N	N	N																				
	1 wk.	b. CPZ 25, one dose	BSP 8	N	6	N																				
	1 wk.	c. CPZ 25, one dose. Pred. 150, 1 day. CPZ 25, 48 hrs. after 1st dose	BSP 8.5	7	7																					
	13 days	d. CPZ 25 daily. To 400 daily in 5 wks. To 800 daily in 16 wks.	BSP — SGP-T N APh —					N 130 5.1		92 4.2		68 N					48			N						

TABLE 2—*Continued*

Case	RI	CPZ Exposures, Mg. Daily	Days After Initial CPZ Dose in Each New Reëxposure																							
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	17	19	20	21	22	25	28	31	38
4	?	*Initial Exposure* (?)																								
62 yrs.		a. CPZ 200 (1 day)		SB 4.4			1.4		1.3						N											
	27 days			BSP —			17		11						6				11							
				SGP-T 146			80		42						N											
		b. CPZ 25, one dose.																								
		Prednisone 150, 5 days.	BSP 10	10	16.5				10																	
	1 wk.	Pre-CPZ: BSP 10.5%																								
		c. CPZ 25, one dose.	BSP 10	19	15			10			11.5															
	27 days	Pre-CPZ: BSP 10%	SGP-T N	73	108			66			N															
		d. CPZ 25 daily. To 300 daily in 10 wks.	BSP —	38	42	—					11.5										8					
		Pre-CPZ: BSP 6%	SGP-T N	115	360	290					46										N					
			APh N	N	4	N																				
			SB N	1.5	1.8	N																				
5	3½ mos.	*Initial Exposure*																								
60 yrs.		a. CPZ 10, 1st day; 25, 2nd day; 25, 3rd day	BSP N	24	25	13	8			7.5		7		6.5			5				9		13		
	7 wks.		SGP-T N	224	236	152	162			76		68		N			N				N		N		
			APh N	6.2	8.8	8.8	5.7			4.6		9.7		N			4.1				8.7		N		
		b. CPZ 10, 25, 25.	BSP N	9	14			6							N											
	11 days	Prednisone 100, 10 days																								
		c. CPZ 10, 25, 25	BSP 8.5	14.5	18.5	10			N																	
			SGP-T N	48	90	86			49		N															
	19 days		APh N	N	4.5	6			4.4		5.4					4.4					N					
		d. CPZ 25 daily. To 200 in 10 wks.	BSP 12.5	30	26				5			—									N		LB.		
			SGP-T N	72	46				44			N												N		
			APh N	6.5	8.4				7.3			5.4									N					

RI: Reëxposure Interval. Time between last preceding dose of CPZ and next reëxposure.
LB: Complete Liver Battery. A complete liver battery was always done wherever an entry of any test has been made. For brevity, most tests have not been recorded if normal. If a test was omitted from a battery, this has been indicated by a dash.
N: Normal.
—: Test not done.

TABLE 2—*Continued*

Case	RI	CPZ Exposures, Mg. Daily		Days After Initial CPZ Dose in Each New Reëxposure																		
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	18	23	24	28
6	6 mos.	*Initial Exposure*																				
66 yrs.		a. CPZ 25, 3 days. Pre-CPZ: BSP 7.5%	BSP	41	63	63	40			19		14		8									
			SGO-T	148	86	55	40			58		N											
			APh	N	N	5.1	4.3			N		N											
	4 wks.		SB	1.3	2.8	1.7	1.7			N		N											
			DB	1.1	1.9	1.1	0.8																
		b. CPZ 25, 22 days; Prednisone 60, 8 days.	BSP	51	19.5	14	7			8.5							8.5				7.5		
		Pre-CPZ: BSP 7.5%	SGO-T	—	—	—																	
	34 days		SB	1.5	N																		
			DB	1.3																			
		c. CPZ 25 daily; to 150 in 1 month.	BSP	26			—				7												
		Stopped after 4 months.	SGO-T	230			N																
	3 mos.	Pre-CPZ: BSP 6%																					
		d. CPZ 100 daily; to 400 in 2 weeks																					
7	5 mos.	*Initial Exposure*																					
65 yrs.		a. CPZ 25, 4 days.	BSP	8.5	20	34	36	39			12		10		9								6.8
		Pre-CPZ: BSP 6.5%	SGO-T	N	103	162	176	88			46		N										
			APh	N	5	6.6	13	8			8.2		7.7		6.3								4.6
	4 wks.		SB	N	N	N	N	1.3			N												
			DB					1.2															
		b. CPZ 25, 22 days; Prednisone 60, 8 days.	BSP	7.6	18.5	13	11			12.5		8					6			6			
			SGO-T	—	—	72	134			N		N					N			N			
	34 days	Pre-CPZ: BSP 6.8%; APh 4.6 B.U.	APh	4.3	4	N	N			4.3		4.3					4.7			N			
		c. CPZ 25 daily; to 150 in 4 months.	BSP	16			—					5											
		Pre-CPZ: BSP 8%	SGO-T	79			48					N											
			APh	5			4.6					N											

TABLE 2—*Continued*

Case	RI	CPZ Exposures, Mg. Daily	Days After Initial CPZ Dose in Each New Reexposure																		
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	18	23	24	28
8	4 mos.	*Initial Exposure*																				
26 yrs.		a. CPZ 25, 1st day; 300, 2nd day. Cortisone 100, 11 days	BSP —	—	—					7.5						N						
	3 yrs.		SB —	4.6	5.7					N						N						
			APh —	—	6					—						—						
			SGP-T —	—	—					—						—						
		b. CPZ 25, one dose	BSP 12	N			N															
	2 wks.		SGP-T 344	198			136							N								
	3 wks.	c. CPZ 25, one dose	SGP-T 63	63																		
		d. CPZ 25 daily; to 800 in 23 days; to 1,200 in 6 weeks	BSP 6			N			LB. N								LB. N					
9	14 wks.	*Initial Exposure*																				
33 yrs.		a. CPZ 150, 2 days		Icteric	SB 5			SB 1.7				N										
	5 wks.							BSP 25				5									N	
								SGO-T —														
		b. CPZ 150, 1 day (Abd. pain 5 hrs. after 1st dose)	BSP 14.5	11.3			N	APh —														
	40 mos.		SGO-T —																			
			APh —																			
		c. CPZ 25, one dose	BSP 8																			
	4 days		SGP-T 79																			
	6 days	d. CPZ 25, and 25, 72 hrs. later	LB. N			BSP 6																
		e. CPZ 50 daily; to 300 in 13 days; to 400 in 5 weeks		LB. N			N				BSP 6.5%			N				LB. N		LB. N		
10	9 mos.	*Initial Exposure*																				
38 yrs.		a. CPZ 150, 5 days; 200, 24 days. Concurrent cortisone 200 daily, 33 days.	BSP 11	18.5	16	15				6.5											6.8	
	8 days	Pre-CPZ: BSP 6%; APh 5 B.U.	SGO-T —	—	—	—															—	
			APh —	—	5.1	—															—	
		b. CPZ 150, 4 days; 200 daily. To 600 daily in 5 months. Pre-CPZ: BSP 5%						BSP 4							7			7				

TABLE 2—*Continued*

Case	Initial Exposure to CPZ, Mg. Daily	First Hepatic Reaction to CPZ	RI	CPZ Reëxposure, Mg. Daily	Days After Initial CPZ Dose in Reëxposure												
					2	3	4	5	6	7	8	9	10	12	13	20	23
11 31 yrs.	CPZ 400, 10 days	Anicteric dysfunction. SB 1.3; BSP 16%	6 wks.	CPZ 100, 2 days	BSP 25 SB 1.6 SGP-T — APh —			8 N — —							N N — —		
12 44 yrs.	CPZ 150, 8 days	Abdominal pain, fever	3 yrs.	CPZ 150, 1 day. T 101° F. and abdominal pain 10 hrs. after first dose	SB 1.9 BSP 20 SGO-T 111 APh 4.6				N 11.5 N 8.4		N 6.5 N 7		N 6.5 N 6.6		N 6 N 4.3		N N N 4.4
13 41 yrs.	CPZ 400, 13 days	Latent sensitization?	15 days	CPZ 200, 1 day. Nausea and abd. pain, 6 hrs. after first dose. T 101.6° F. 24 hrs. after first dose	SB 1.76 BSP 32 SGP-T 700	N — 655		10 340				N 111		76			N
14 42 yrs.	CPZ 100, 15 days	Jaundice SB 7.3	3 mos.	CPZ 100, 30 days. Concurrent hydrocortisone 100, 38 days. Five weeks later, CPZ 100, increasing to 800, without hepatic dysfunction	BSP N SGP-T — APh — SB N	N — — N				N — — N			N — — N				
15 37 yrs.	CPZ 75–200, 14 days	Jaundice SB 2.7	7 wks.	CPZ 25, 1st day; 100, 2nd day; increased to 200 daily. Administered 4 yrs. to date					LB. N						LB. N		
16 39 yrs.	CPZ 150–400, 24 days	Jaundice SB 11	3 mos.	CPZ 150, 14 days; 300–450 daily, 3 months	LB done two months after first dose: N												
17 29 yrs.	CPZ 150–300, 13 days	Jaundice SB 3.2	3 wks.	CPZ 50, 11 days. 1 month later, CPZ 50 increasing to 600. Administered for 26 months	LB not done. No overt hepatic reaction												

remaining patients, chlorpromazine was stopped in one when fever and abdominal pain occurred on the eighth day of treatment (case 12), a second voluntarily ceased ingesting the drug after the thirteenth day (case 13), and a third, to whom 75 mg. daily had been administered for three days only, manifested frank jaundice five days after the last dose (case 5).

Fifteen days to three years after the last internal contact with chlorpromazine, the drug was re-administered to this group (table 2). The daily dose for all except one (table 2, case 9, challenge a; table 6, case 9) was either equal to or, usually, much smaller than the daily dose administered originally. Within 24 to 48 hours after commencing the challenge, acute hepatic dysfunction was provoked in 10. Two of the 16 patients did not develop hepatic dysfunction after each had been given a single dose of

TABLE 3

Time Interval from Original Initiation of Chlorpromazine to First Episode of Hepatic Dysfunction (a), Compared with Time Interval from Start of Challenge to Demonstration of Accelerated Hepatic Dysfunction (c): 11 cases

Longest interval (b) in each of 13 cases between last preceding exposure to chlorpromazine and subsequent challenge provoking accelerated hepatic dysfunction (c).

Case (Numbered as in Table 2)	1	3	13	4	11	5	7	6	10	2	8	12	9
a. Days from original initiation of CPZ to occurrence of first episode of hepatic dysfunction	12	29			10	8	8	16	21	15	8	8	13
b. Longest interval	1 wk.	1 wk.	2 wks.	1 mo.	1½ mos.	3½ mos.	5 mos.	6 mos.	9 mos.	13 mos.	3 yrs.	3 yrs.	40 mos.
c. Days from start of challenge to demonstrated reproduction of dysfunction	1	1	2	2	2	2	2	1	1	2	1	2	1

chlorpromazine (25 mg.), accompanied and followed by prednisone (150 mg. daily). Later, when each was given only the challenging dose of 25 mg., hepatic dysfunction occurred within the next 24 hours (table 2, cases 1, 3).

In the remaining four of the 16 patients, hepatic dysfunction was not demonstrated. Inadequate or no liver function studies were done in three (table 2, cases 15, 16, 17). The fourth, adequately studied, received chlorpromazine, 100 mg., and hydrocortisone, 100 mg., concurrently daily for one month (table 2, case 14).

A seventeenth patient should be added to this group (table 2, case 4). One day after he had ingested the first of two doses of chlorpromazine (100 mg.), fever occurred (102° F.). Next day, jaundice was apparent. Previous exposure to chlorpromazine or a phenothiazine derivative was suspected but not proved. Later, re-administration of chlorpromazine (25 mg.) provoked hepatic dysfunction within 48 hours.

Thirteen of 17 patients, then, who had completely or almost completely recovered from hepatic dysfunction, or who presumably had latent sensi-

tization, developed acute dysfunction within 24 to 48 hours after reëxposure to chlorpromazine.

Of these 13 patients, each of nine had two to four episodes of dysfunction provoked upon reëxposure to chlorpromazine at intervals varying from one week to 40 months (tables 2, 3). Eight of the nine patients developed one to three of these episodes within 24 hours after challenge was initiated, and the rest of the episodes occurred within 48 hours. The ninth patient did not manifest dysfunction within 24 hours, but did so within 48 hours (table 2, case 4).

Of the remaining four patients, each was challenged once. In one, hepatic dysfunction developed within 24 hours after initiation of challenge (table 2, case 10). In three, the liver function tests were not done until 48 hours after initiation of challenge. Dysfunction was then manifest (table 2, cases 11, 12, 13).

Influence of Size and Duration of Chlorpromazine Challenge Upon Intensity of Hepatic Response

Nine challenges of chlorpromazine (25 mg.), unaccompanied by corticosteroid, were administered to six patients, with intervals from the last drug exposures varying from one week to 40 months (table 2, case 1, challenges b, d; case 2, challenges b, d; case 3, challenge b; case 4, challenge c; case 8, challenges b, c; case 9, challenge c). Seven of the challenges provoked asymptomatic anicteric hepatic dysfunction within 24 hours, and two did so within 48 hours. Occurrence of maximal dysfunction varied from 24 to 72 hours after challenge. Dysfunction was manifested by an abnormal increase of bromsulfalein retention (8 to 19%) and serum transaminase (SGP-T, 63 to 344 units), occurring alone or together. Four reactions subsided within one week, five within two weeks.

Four challenges of chlorpromazine (25 mg. daily for two to four days, unaccompanied by corticosteroid) were administered to three patients, with intervals from the last drug exposures varying from 11 days to six months (table 2, case 5, challenges a, c; case 6, challenge a; case 7, challenge a). Asymptomatic anicteric or slightly icteric hepatic dysfunction developed within 24 hours after initiation of three of the challenges, and within 48 hours after initiation of one. In three of the reactions, dysfunction became maximal within 24 to 48 hours after the final dose of chlorpromazine. In the fourth reaction, maximal dysfunction appeared one day after the second dose and began to decline one day after the third, final dose.

In all of the four reactions, there was an abnormal increase of bromsulfalein retention (18.5 to 41%, without hyperbilirubinemia), serum transaminase (SGP-T, 90 to 236 units), and alkaline phosphatase (5.1 to 13 Bodansky units). In two reactions there was an increase of total serum bilirubin (1.3 and 2.8 mg.). No reaction subsided within one week, two did so within three weeks, and two had not after one month.

Six challenges of chlorpromazine were administered to five patients for one or two days, the daily dosage ranging from 100 to 200 mg. (table 2, cases 4, 9, 11, 12, 13). The last drug exposures had occurred two weeks to three years before (interval unknown, case 4). Five to 10 hours after the initial dose had been administered, nausea and abdominal pain occurred in three patients (cases 9, 12, 13). Ten to 24 hours after the initial dose, fever (101 to 102° F.) occurred in three (cases 4, 12, 13). Within 36 to 48 hours after the initial dose, subclinical jaundice was present in three (cases 11, 12, 13) and frank jaundice in two (cases 4, 9).

In summary: following latent sensitization or recovery from the initial episode of hepatic dysfunction due to chlorpromazine, a challenging dose provoked hepatic dysfunction within 24 to 48 hours in 13 of 17 cases (76%), even as long as 40 months after the last drug exposure. The larger or more prolonged the challenge, the more intense the reaction provoked, sometimes with prodromal nausea, abdominal pain and fever developing five to 10 hours after the start of challenge.

Rarely, after an initial partial subsidence of provoked dysfunction, a moderate recrudescence occurred (table 2, case 5, challenge a; case 2, challenge c).

Suppressive Effect of Synthetic Adrenocortical Hormone Prophylactically Administered, Upon Hepatic Response to Chlorpromazine Challenge in Five Cases (Table 4)

Two to four chlorpromazine challenges were administered to each of five patients. For four patients, each challenge consisted of a single dose of 25 mg. For the fifth, each challenge consisted of a three-day course of 10 mg., 25 mg. and 25 mg. (table 4).

In each case, alternate challenges of chlorpromazine were accompanied by prednisone, 100 to 150 mg. daily, in divided doses at 12-hour intervals. Prednisone was begun 15 or 24 hours before chlorpromazine was administered, and then continued for three to six days after completion of the challenge (exception: table 2, case 3, challenge c; table 4, case 3). Intervals between reëxposures to chlorpromazine ranged from one to 12 weeks.

In four cases, prednisone inhibited hepatic response to challenge, as reflected by serum transaminase and alkaline phosphatase levels. Hepatic reactivity, as reflected by bromsulfalein retention, was little if at all repressed.

In the fifth case, hepatic responses to challenging doses were minimal, and the influence of prednisone was equivocal (case 3).

There were seven prednisone-covered challenges. Three provoked no hepatic responses, and four provoked dysfunction within 24 to 72 hours. Bromsulfalein retention was increased after the four challenges (8.5 to 16.5%), and one of them also provoked slight elevation of serum transaminase (SGP-T, 44 units). Five abnormal liver function tests, then, followed seven prednisone-covered challenges.

TABLE 4

Inhibiting Effect of Large Doses of Prednisone, Prophylactically Administered, upon Hepatic Responses to Chlorpromazine Challenges; Five Cases

Case No. as in Table 2	Preceding Hepatic Reaction Induced by CPZ	RI*	Challenge, Mg. Daily	Maximal Hepatic Reaction†	RI	Challenge, Mg. Daily	Maximal Hepatic Reaction	RI	Challenge, Mg. Daily	Maximal Hepatic Reaction	RI	Challenge, Mg. Daily	Maximal Hepatic Reaction
4	Jaundice	LONG 4 wks.	CPZ 25, one dose. Pred. 150, 5 days	MILD BSP 16.5%	SHORT 1 wk.	CPZ 25, one dose	STRONG BSP 19% SGP-T 108						
1	Anicteric dysfunction	LONG 3 wks.	CPZ 25, one dose. Pred. 150, 6 days	None	SHORT 1 wk.	CPZ 25, one dose	STRONG SGP-T 208	LONG 3 wks.	CPZ 25, one dose. Pred. 150, 6 days	None	SHORT 1 wk.	CPZ 25, one dose	STRONG SGP-T 79
3	Jaundice	LONG 6 wks.	CPZ 25, one dose. Pred. 150, 6 days	None	SHORT 1 wk.	CPZ 25, one dose	STRONG BSP 8%	SHORT 1 wk.	CPZ 25, one dose. Pred. 150, 1 day	STRONG BSP 8.5%			
2	Anicteric dysfunction	LONG 16 wks.	CPZ 25, one dose	STRONG BSP 17% SGP-T 82	SHORT 3 wks.	CPZ 25, one dose. Pred. 150, 6 days	MILD BSP 10% SGP-T 44	LONG 12 wks.	CPZ 25, one dose	STRONG BSP 14% SGP-T 79			
5	Jaundice	LONG 14 wks.	CPZ 10, 25, 25	STRONG BSP 25% SGP-T 236 APh 8.8	SHORT 7 wks.	CPZ 10, 25, 25. Pred. 100, 10 days	MILD BSP 14%	SHORT 1½ wks.	CPZ 10, 25, 25	STRONG BSP 18.5% SGP-T 90 APh 6			

*RI = Reëxposure interval: number of weeks between last preceding dose of CPZ and next challenge. Indicated as LONG or SHORT relative to other RIs in a case.
† STRONG or MILD = intensity of hepatic reactions relative to one another in each case.

Eight challenges of chlorpromazine without prednisone all provoked hepatic dysfunction within 24 to 48 hours. In six hepatic responses, bromsulfalein retention increased (8 to 25%); in seven, serum transaminase increased (SGP-T, 79 to 236 units); in two, serum alkaline phosphatase increased (6 and 8.8 Bodansky units). Fifteen abnormal liver function tests, then, followed eight challenges of chlorpromazine unaccompanied by prednisone.

In the analysis of the inhibiting effect of prednisone, two factors were scrutinized for their possible influence upon hepatic responsiveness to a chlorpromazine challenge. These were: (1) the factor of time—the relatively short and long spans, in each case, between a chlorpromazine challenge and the prednisone-covered challenge which preceded or followed it; (2) the usual tendency for a challenge to provoke, on repetition, a hepatic reaction milder and briefer than its predecessor.

The following data appeared to exclude the factor of the time interval between challenges as possibly confusing the evaluation of the influence of prednisone. Four prednisone-covered challenges which followed exposures to chlorpromazine after relatively "long" spans of time (three, three, four and six weeks) provoked relatively "mild" or no hepatic reactions (cases 4, 1, 3). Three challenges of chlorpromazine without prednisone which followed exposures to chlorpromazine after relatively "long" intervals (12, 14 and 16 weeks) provoked relatively "strong" hepatic reactions (cases 2 and 5).

Three prednisone-covered challenges which followed exposures to chlorpromazine after relatively "short" intervals (one, three and seven weeks) provoked two relatively "mild" hepatic reactions, and one reaction equivalent to its predecessor (cases 5, 2 and 3). Five challenges of chlorpromazine which followed prednisone-covered challenges after relatively "short" intervals (one, one, one, one, and one and one-half weeks) provoked relatively "strong" hepatic reactions (cases 4, 3, 1, 5).

When compared with hepatic dysfunction provoked by the prednisone-covered challenge, the dysfunction provoked by the subsequent challenge of chlorpromazine was always "stronger." This fact appeared to exclude decreasing hepatic reactivity to successive challenges as a possibly confusing factor in the evaluation of the influence of prednisone.

In contrast, the course of established jaundice due to chlorpromazine was unaltered in three patients by the therapeutic administration of synthetic adrenocortical hormone (table 5).

Deliberate Desensitization

In 10 patients, chlorpromazine was discontinued upon the appearance of icteric or symptomatic anicteric hepatic dysfunction. After they had completely or almost completely recovered from dysfunction, deliberate desensitization was undertaken (tables 2 and 6). Time intervals from the last

dose of chlorpromazine to the onset of desensitization ranged from three weeks to 40 months.

As our experience grew, methods of desensitization were modified. They were also shaped and somewhat prolonged by concurrent studies concerning the evolution of accelerated hepatic dysfunction provoked by challenging doses of chlorpromazine, and the prophylactic effect of synthetic adrenocortical hormones upon this reaction. The methods evolved in three broad groups.

TABLE 5

Lack of Therapeutic Effect of Synthetic Adrenocortical Hormone upon the Course of Three Cases of Established Jaundice Induced by Chlorpromazine

Case 1. Age 32 yrs. (Tables 2, 6, Case 2)				*Case 2.* Age 34 yrs.			*Case 3.* Age 40 yrs.				
Days after CPZ Stopped	S.B.	SGO-T	Hormone, Mg. Daily	Days after CPZ Stopped	S.B.	Hormone, Mg. Daily	Days after CPZ Stopped	S.B.	SGP-T	APh	Hormone, Mg. Daily
1	1.6			1	8.4		1	1.7	260	5.4	
13	9.9						6	8.1	520	4.9	Pred. 150 8 days
19	7.6						14	21	1,040	4.8	50, 4 days
26	10	353	Pred. 100 12 days	12	20	Cortisone 200, 7 days	18	25	1,310	5.2	20, 2 days
33	8.2	168					20	22	420	9.4	10, 1 day
38			40, 4 days								
40	6.8	205		19	30	Discont'd.	21				5, 3 days
42			10, 3 days				23	26	520	9.9	Discont'd.
44			Discont'd.				26	29	350	9.3	
47	6.9	156		26	32.6						

GROUP I

Desensitization was first attempted by administering chlorpromazine and synthetic adrenocortical hormone daily and concurrently. This method was based on the premise that the hormone might, by interfering with an immunologic reaction, inhibit hepatic dysfunction provoked by challenge, and on the report that it did not interfere with desensitization in another system.[3] There were four patients in this group.

Tables 2 and 6, Case 8. Jaundice had resulted from the daily administration of chlorpromazine, 150 to 300 mg. for eight days. Four months later, with hepatic recovery complete, cortisone, 100 mg. daily, was begun. Twenty-five milligrams of chlorpromazine were then administered on one day and 300 mg. on the next day. Vomiting, fever and frank jaundice developed within 48 hours after administration of the first dose.

The attempt at desensitization in this case was abandoned for three years.

Table 2, Case 14. Jaundice had resulted from the daily administration of chlorpromazine, 100 mg. for 15 days. Three months later, with hepatic recovery complete, the daily concurrent administration of hydrocortisone,

100 mg. and chlorpromazine, 100 mg., was begun and continued for one month. Hepatic dysfunction did not occur. Five weeks after both drugs had been stopped, chlorpromazine, 100 mg. daily, was resumed, and was increased to 800 mg. daily. Dysfunction did not occur.

In the absence of a hepatic reaction, it could not be concluded that hepatic hypersensitivity to chlorpromazine had not spontaneously disappeared before desensitization was begun.

Tables 2 and 6, Case 10. Jaundice had resulted from the daily administration of chlorpromazine, 200 mg. for 21 days. Nine months later, slight hepatic dysfunction persisted, with bromsulfalein retention, 6%, and alkaline phosphatase, 5 Bodansky units. Daily concurrent administration of cortisone, 200 mg., and chlorpromazine, 150 to 200 mg., was begun. Within 24 hours after the first dose of chlorpromazine had been administered, bromsulfalein retention began to rise, reached a maximum of 18.5% within 48 hours, then subsided within a week. Administration of cortisone and chlorpromazine was discontinued after one month. After a lapse of eight days, chlorpromazine, 150 mg. daily, was reinstituted, and slowly increased to 600 mg. daily, without hepatic reaction.

Here, deliberate desensitization had been achieved with only slight, transient, accelerated hepatic dysfunction having been provoked, and cortisone had not appeared to interfere with the mechanisms of desensitization.

Tables 2 and 6, Case 2. Jaundice had resulted from the daily administration of chlorpromazine, 300 to 600 mg. for 15 days. Thirteen months later, a plateau of hepatic dysfunction persisted, with bromsulfalein retention, 11.5%, and SGP-T, 66 units.

Prednisone, 150 mg. daily, was begun, and after six days chlorpromazine, 5 mg. daily, was begun. Within 48 hours after the first dose of chlorpromazine had been administered, SGP-T rose to 98 units. During the ensuing month, as the daily chlorpromazine dosage was very slowly increased to 25 mg., SGP-T slowly rose to 154 units. During the subsequent three weeks, chlorpromazine, mg. 30 daily, was administered, while prednisone was very slowly decreased to 5 mg. daily. At that time, when prednisone and chlorpromazine were simultaneously stopped, bromsulfalein retention was 38%, SGP-T was 820 units, and alkaline phosphatase, 8.6 Bodansky units. Total serum bilirubin was normal, but the one-minute direct bilirubin was 0.96 mg.

The attempt at desensitization was abandoned as a failure. It was concluded that an elevated serum transaminase forecast unsuccessful desensitization. Four months later, with hepatic function normal, another attempt (described under Group III) was successful.

Group II

A much smaller initial challenge with chlorpromazine alone was administered. After recovery from the accelerated hepatic dysfunction provoked,

a long course of daily chlorpromazine was instituted, with concurrent administration of prednisone for the initial eight days only.

There were two patients in this group. In one (tables 2 and 6, case 7), a maculopapular rash and anicteric hepatic dysfunction had resulted from the daily administration of chlorpromazine, 50 mg. for eight days. In the second (tables 2 and 6, case 6), jaundice was noted after the daily administration of chlorpromazine, 150 mg. for 16 days.

Five and six months later, with persisting bromsulfalein retention of 6.5% and 7.5%, chlorpromazine, 25 mg. daily, was re-administered for three and four days, respectively. Within 24 hours after the first dose, asymptomatic hepatic dysfunction appeared, became maximal and slightly icteric within two and five days, and then subsided in approximately two weeks.

Four weeks after the last dose of chlorpromazine, 25 mg. daily were begun; and prednisone, 60 mg. daily, in divided doses every eight hours, was concurrently administered for the initial eight days. Within 24 and 48 hours after the first dose of chlorpromazine, asymptomatic anicteric hepatic dysfunction occurred. It subsided within two weeks. After prednisone was stopped, chlorpromazine, 25 mg. daily, was continued alone for two weeks longer, without further exacerbation of hepatic dysfunction.

Here it appeared that deliberate desensitization to 25 mg. daily had been achieved. To evaluate the permanence of this tolerance, chlorpromazine was discontinued for 34 days. The resumption of 25 mg. daily provoked, in both cases, asymptomatic anicteric hepatic dysfunction within 24 hours after the initial dose. These reactions, although milder and briefer than their immediate predecessors, demonstrated deterioration of the state of tolerance previously achieved to that dosage. Dysfunction subsided within a few days while chlorpromazine was continued. It was gradually increased to 150 and 400 mg. daily, respectively, without further hepatic reaction.

Thus far, several facts had emerged. The smaller the challenging dose, the milder the dysfunction provoked. Concurrent administration of adrenocortical hormone did not interfere with the mechanisms of hepatic desensitization. After subsidence of dysfunction provoked by challenge, the next challenge tended to elicit a milder hepatic reaction. A state of tolerance to a small (25 mg.) daily dose of chlorpromazine, having been established for a few weeks only, tended to deteriorate if the drug was then discontinued for five weeks.

Group III

Six patients were each challenged with a single dose of chlorpromazine, 25 mg. three weeks to 40 months after their last preceding exposure to the drug (tables 2 and 6, cases 1, 2, 3, 4, 8, 9). Another patient was challenged with a three-day course of 10 mg., 25 mg. and 25 mg. (tables 2 and 6, case 5).

Each of the seven was challenged two to four times at intervals ranging from four days to 12 weeks. Usually a challenge was repeated soon after the dysfunction provoked by the preceding challenge had subsided.

Six days to four weeks after hepatic dysfunction had been provoked by the last challenge, a long course of chlorpromazine, 25 mg. daily, was started in six of the patients. Asymptomatic anicteric hepatic dysfunction occurred in four (table 2, cases 1, 3, 5, 8). Slightly icteric hepatic dysfunction occurred in the fifth (case 4). Reactions began within 24 to 48 hours after the first dose, became maximal within 24 to 72 hours (usually the latter), and subsided within approximately four to 14 days.

The sixth patient (case 2) was begun on his long course only one week after hepatic dysfunction had been provoked by challenge. This reaction had not yet subsided completely. There was no exacerbation of dysfunction upon the initiation of the long course. Normal function returned within two months, even while the daily dose of chlorpromazine was steadily increased.

The final patient (case 9) was begun on chlorpromazine, 50 mg. daily, only six days after the last preceding challenge had provoked slight hepatic dysfunction. He was rapidly increased to 200 mg. daily within five days. This briefly provoked a slight rise of bromsulfalein retention.

From this point on, increases in the daily dose of chlorpromazine were controlled by one basic principle: to increase the dose only if there was present normal hepatic function or a degree of dysfunction like that immediately antedating the start of desensitization. In the earlier cases we were quite cautious, sometimes delaying an increase for weeks after such states of hepatic function had been demonstrated.

In all cases, the daily dosages finally established were either equal to or, more usually, larger than those which had elicited the original episodes of hepatic dysfunction. At present, these dosages have been uneventfully administered to 10 cases for periods varying from two and one-half months to more than three years. There have been no adverse effects (table 6).

It cannot be stated whether the slight dysfunction persisting in a few cases (table 6, cases 4, 6, 7) represented residual from the initial bout of dysfunction induced by chlorpromazine, or antedated the prime drug exposure.

In three cases (table 6, cases 1, 5, 6), after daily dosages of 150 to 600 mg. had been administered for periods ranging from 11 weeks to nine months, chlorpromazine was discontinued for three to five months. Administration of the drug was then resumed, and these daily doses were rapidly approximated or exceeded without evidence of recurrent dysfunction, demonstrating that a state of tolerance to these daily dosage levels had been preserved for as long as five months after chlorpromazine had been stopped.

TABLE 6

Deliberate Hepatic Desensitization to Chlorpromazine; 10 Cases

Case No. as in Table 2	CPZ Mg. Daily; No. Days Given Until Initial Hepatic Reaction	Maximal Hepatic Dysfunction	Residual Dysfunction Just Prior to First Challenge	Number of Challenges Preceding Long Course of Desensitization	Long Course of CPZ, Mg. Daily	Type and Duration of Hepatic Reaction Provoked by Long Course	Interruption of Long Course; Duration
1	400; 12 days	SB 1.1 mg. BSP 30% SGP-T 116 APh 4.4 B.U.	None	4	CPZ 25, increasing to 600 in 1 mo.	Anicteric, <9 days	After 11 wks. of CPZ, discontinued for 5 mos.
2	300–600; 15 days	SB 10 mg.	None	4	CPZ 25, increasing to 600 in 6 wks.	None	None
3	600–800; 29 days	SB 7.4 mg	None	3	CPZ 25, increasing to 800 in 4 mos.	Anicteric, c. 2 weeks	None
4	200; 1 day	SB 4.4 mg.	BSP 10.5%	2	CPZ 25, increasing to 300 in 10 wks.	Anicteric, c. 10 days	None
5	75; 3 days	SB 16 mg.	None	3	CPZ 25, increasing to 200 in 10 wks.	Anicteric, c. 2 weeks	After 9 mos. of CPZ, discontinued for 4 mos.
6	150; 16 days	SB 10 mg.	BSP 7.5%, CF 3+	1	CPZ 25, 22 days. Pred. 60 mg./day, concurrent for 1st 8 days	Anicteric, 4 days	a. After 22 days of CPZ, discontinued for 1 mo. b. After 15 wks. of CPZ, again discontinued for 3 mos.
7	50; 8 days	SB 1.1 mg. BSP 29% SGO-T 120 APh 14 B.U.	BSP 6.5%	1	CPZ 25, 22 days. Pred. 60 mg./day, concurrent for 1st 8 days	Anicteric, <3 wks.	After 22 days of CPZ, discontinued for 1 mo.
8	150–300; 8 days	SB 11 mg.	None	3	CPZ 25, increasing to 1,200 in 6 wks.	Anicteric, <3 days	None
9	100; 13 days	SB 3.5 mg.	None	4	CPZ 50, increasing to 400 in 5 wks.	Anicteric, <7 days	None
10	200; 21 days	SB 9 mg.	BSP 6% APh 5 B.U.	None	CPZ 150–200, 30 days. Concurrent cortisone 200 daily, 33 days	Anicteric, c. 7 days	After 1 mo. of CPZ, discontinued for 8 days

TABLE 6—*Continued*

Case No. as in Table 2	Renewal of Long Course	Type and Duration of Hepatic Reaction Provoked by Renewal of CPZ	Duration of Long Course	Maximal CPZ, Mg. Daily	Present Status of CPZ Rx	Latest Liver Battery	Comment
1	CPZ 100, increasing to 400 in 6 days	None	8 mos.	600	Current, 400/day	Normal, after 7 mos. daily CPZ	
2			5 mos.	600	Current, 600/day	Normal, after 5 mos. daily CPZ	
3			13 mos.	800	Current, 800/day	Normal, after 13 mos. daily CPZ	
4			15 mos.	300	Current, 300/day	BSP still 11% after 14 mos. daily CPZ	
5	CPZ 100	None	16 mos.	200	Current, 100/day	Normal, after 10 mos. daily CPZ	
6	a. CPZ 25, increasing to 150 in 1 mo. b. CPZ 100, increasing to 400 in 2 wks.	a. Anicteric, c. 3 days b. No overt reaction (batteries not done upon 2nd renewal)	6 mos.	400	Terminated	At termination, BSP still 6%, CF 3+ 7 mos. after termination, BSP 8.5%, CF 3+	Five months after termination, liver biopsy normal
7	CPZ 25, increasing to 150 in in 4 mos.	Anicteric, <1 wk.	16 mos.	150	Terminated by death (pneumonia)	BSP still 6%, after 14 mos. daily CPZ	Post mortem: liver negative except for terminal changes and some focal and somewhat variable lymphocytic infiltration into many but not all portal areas. (Sequela of an earlier inflammatory reaction?)
8			4 mos.	1200	Current, 800/day	Normal, after 4 mos. daily CPZ	
9			2½ mos.	400	Current, 400/day	Normal, after 2½ mos. daily CPZ	
10	CPZ 150, increasing to 600 in 5 mos.	None	3 yrs.	600	Current, 600/day	Normal, after 3 yrs. daily CPZ	Liver biopsy normal, after 2½ years daily CPZ

Specificity

Jaundice similar to that induced by chlorpromazine has sometimes been caused by mepazine,[4, 5] prochlorperazine [6] and promazine.[7]

These and/or other phenothiazine derivatives were administered to seven patients from three to 35 months after recovery from chlorpromazine-induced jaundice (table 7). With one exception (case 1), the drugs were uneventfully tolerated and were administered in full dosage for periods varying from 15 days to 17 months without the occurrence of hepatic dysfunction.

One patient received promazine; one, prochlorperazine; one, promazine and prochlorperazine; one, mepazine; one, perphenazine; one, mepazine and perphenazine; and one, promazine, perphenazine and trifluoperazine.

The last patient (table 7, case 1) manifested cross-reactivity between chlorpromazine and promazine, for hepatic dysfunction appeared within 24 hours after promazine therapy was begun.[24] Structurally, promazine differs from chlorpromazine only in lacking a chlorine radical. In an individual sensitized to a drug, this phenomenon of cross-reactivity may be elicited by other chemicals quite similar to the drug in structural configuration. Cross-reactivity did not occur upon subsequent administration to this patient of perphenazine and trifluoperazine. Compared with promazine, these drugs are less similar to chlorpromazine in structural configuration.[36] All share the phenothiazine nucleus. Chlorpromazine and promazine have the same aliphatic "tails." Trifluoperazine and perphenazine have aromatic "tails," including a piperazine ring.

Three years after this patient's last exposure to chlorpromazine, and after months of uneventful treatment with perphenazine and trifluoperazine, he was given one challenging dose of chlorpromazine (25 mg.). Within 24 hours, hepatic dysfunction occurred (table 7, case 1). Desensitization to this drug was then effected, and eventually 800 mg. daily were tolerated (tables 2 and 6, case 8).

Specificity appears to have been demonstrated in this group. Those who develop hepatic dysfunction due to chlorpromazine do not thereafter react nonspecifically to any drug known to have a tendency to cause liver damage.

Skin Tests

At various stages during or following a bout of jaundice due to chlorpromazine, each of 18 of our patients was injected intradermally with 0.1 c.c. serum freshly obtained from patients ingesting 1,000 to 1,600 mg. chlorpromazine daily. Observed every five minutes for the first hour and again at 24 hours, the skin tests were negative.

Skin tests were also carried out according to the technic of Prausnitz-Küstner. Sera obtained from three acutely jaundiced patients and from two patients a few weeks after recovery from jaundice were injected intra-

TABLE 7

Specificity of Hepatic Dysfunction due to Chlorpromazine

Case	Initial Hepatic Reaction to CPZ	Reëxposure to CPZ (Mg. Daily) Duration	Hepatic Reaction	Promazine (Mg. Daily) Duration	Hepatic Reaction	Other Phenothiazines (Mg. Daily) Duration	Hepatic Reaction	Reëxposure to CPZ	Hepatic Reaction
1. (Tables 2, and 6, Case 8)	Jaundice (4/56)	25, 1st day 300, 2nd day (8/56)	Within 36 hours	150, 5 days (10/56)	Within 24 hours	Trifluoperazine 40–80, 5 weeks (2/59–3/59)	None	25 mg., (10/59)	Within 24 hours
						Perphenazine 16–48, 3 months (3/59–6/59)	None		
						Trifluoperazine 20–40, 5 months (6/59–11/59)	None		
2. (Table 2, Case 11)	Jaundice (3/56)	100, 2 days (5/56)	Within 48 hours	50, 2 months (11/56–1/57)	None				
3.	Jaundice (8/56)	25, 3 days (9/56)	No overt reduction (liver tests not done)	100–1600, 9 months (11/56–8/57)	None	Prochlorperazine 60–120, 3 weeks (8/57–9/57)	None		
						Prochlorperazine 40–75, 6 months (1/58–7/58)	None		
4.	Jaundice (3/56)	No				Prochlorperazine 20–150, 9 months (3/58–12/58)	None		
5. (Table 2, Case 16)	Jaundice (12/55)	150–450, 3½ months (3/56–6/56)	None (liver batteries begun 2 months after first reëxposure)			Mepazine 150, 15 days (11/57)	None		
6. (Tables 2 and 6, Case 6)	Jaundice (3/57)	25–150, (9/57–4/58)	Within 24 hours (desensitization achieved)			Perphenazine 32–64, 5 months (4/58–9/58)	None	100–400, 2 months (7/58–9/58)	No overt reaction
7. (Table 2, Case 17)	Jaundice (7/56)	50, 11 days (8/56)	No overt reaction (liver tests not done until 6/58)			Mepazine 75–100, 17 months (2/57–7/58)	None		
		200–600, 26 months (9/56–11/58)				Perphenazine 32, 1 month (6/58–7/58)	None		

dermally into each of three patients who had never received chlorpromazine. Sera freshly drawn from patients ingesting 1,200 to 1,600 mg. chlorpromazine daily were employed as antigen. Observed every five minutes for the first hour and again at 24 hours, the tests were negative.

In 12 patients, during or after an attack of jaundice, patch tests for 48 hours with a 3% aqueous solution of chlorpromazine were negative. Intradermal tests with chlorpromazine in saline and serum were variable and difficult to interpret.[8]

Clinical Evolution of Hepatic Dysfunction

In the 13 patients already discussed, 35 episodes of accelerated hepatic dysfunction were provoked by re-administered chlorpromazine. In 11 of the patients, 27 episodes were followed in sufficient detail to permit the following analysis (table 8).

Table 8

Occurrence of Abnormal Results of Liver Function Tests in 27 Episodes of Accelerated Hepatic Dysfunction Provoked by Re-administered Chlorpromazine

BSP (6 to 16.5%) (CF positive: two episodes)	5
Trans. (SGP-T, 56–208 units)	4
BSP and Trans. (CF positive: one episode)	7
BSP, Trans. and APh (CF positive: three episodes)	5
BSP, Trans. and SB (CF positive: one episode)	2
BSP, Trans. APh and SB (CF positive: two episodes)	4

Increased bromsulfalein retention occurred in 23 episodes, increased serum transaminase in 22, increased serum alkaline phosphatase in nine, increased total serum bilirubin in six, and positive cephalin flocculation (2 plus to 4 plus) in nine (three cases).

In five of these episodes, increased bromsulfalein retention occurred alone; in four, serum transaminase occurred alone. Increased alkaline phosphatase never occurred alone, but accompanied or followed rises of bromsulfalein retention and serum transaminase. Increased total serum bilirubin preceded, accompanied, followed, or occurred without a rise of alkaline phosphatase.

Maximal increase of bromsulfalein retention (without hyperbilirubinemia) was 41%; of transaminase (SGP-T), 700 units; of alkaline phosphatase, 13 Bodansky units.

In 26 of the 27 episodes, the duration of dysfunction could be measured with a fair degree of accuracy (table 9). Within two weeks, dysfunction subsided completely in 20. In each of the remaining six, one or two of the following—bromsulfalein retention, serum transaminase, alkaline phosphatase—remained abnormally increased for periods varying from more than two weeks to more than four weeks (table 2, cases 2, 5, 7, 12, 13).

In the earliest development of hepatic dysfunction, increased bromsulfalein retention was the most frequent and usually the most sensitive in-

dicator of its onset. This was usually accompanied or followed within hours by a rise of serum transaminase. Sometimes serum transaminase was the more sensitive or sole indicator. These findings were in harmony with data from earlier studies,[2, 9] and pointed to the hepatic cell as the site of earliest derangement.

The abnormal rises and declines of bromsulfalein retention and serum transaminase usually were fairly concurrent. Occasionally, as noted, one or the other rose alone. Sometimes increased dye retention persisted one to three weeks longer than did an elevation of transaminase (table 2, case 5, challenge a; case 12), or an elevated transaminase persisted one to two weeks longer than an increased dye retention (table 2, case 3, challenge d; case 8, challenge b; case 13).

TABLE 9

Duration of Abnormalities of Liver Function Tests in 26 Episodes of Accelerated Hepatic Dysfunction

No. Days	1–7	8–14	15–21	22–28	29+
BSP	11	8	1		2
Trans.	8	11	1		1
APh	3	2	1	2	1
SB	5	1			
CF	6		1		2

These facts suggest that, in this form of dysfunction, these two biochemical indices of the hepatic state may not be reflecting—with different degrees of sensitivity—the same hepatocellular locus of disturbed metabolic activity; but rather, perhaps, derangements of different functional sectors of the hepatic cell.

With dysfunction intensifying, serum alkaline phosphatase and total serum bilirubin become elevated and frank jaundice finally appears.

As already noted, serum alkaline phosphatase rises only—but not always—when both bromsulfalein retention and serum transaminase have become elevated. It may then be followed by an increase of serum bilirubin, the prompt direct-reacting fraction predominating from the start. However, total serum bilirubin sometimes rises to levels of overt jaundice before or even without a subsequent rise of serum alkaline phosphatase (table 2, case 4). Occasionally, as hyperbilirubinemia begins to subside, an increased serum alkaline phosphatase rises even higher.[10]

There appears to be no correlation between the levels of total serum bilirubin and of alkaline phosphatase. In the absence of hyperbilirubinemia, the level of serum alkaline phosphatase may rise above 10 Bodansky units, and in the presence of overt jaundice it may remain within normal limits. In 17 of 23 cases, it failed to rise to 10 Bodansky units at any time during the phase of increasing or maximal hyperbilirubinemia (table 10).

A detailed study has not been made of the behavior of total serum

cholesterol and esters in this disorder. In approximately 70% of cases, after jaundice is well marked, total serum cholesterol may increase, with the esterification ratio normal.[10] Only once, in a patient with marked jaundice (SB, 27 mg.), did we observe the ratio briefly decline to a range of 25 to 40%.[10]

Cephalin flocculation infrequently and thymol turbidity rarely have become positive early in the development of dysfunction, and have usually become negative sooner than other laboratory evidences of hepatic dysfunction.[2, 10, 20]

TABLE 10

Case	Maximal SB mg./100 ml.	Maximal APh During Phase of Increasing or Maximal SB
1	1.3	13
2	1.3	5.1
3	1.4	3.4
4	1.76	3
5	1.9	4.6
6	2.7	4.5
7	2.8	13
8	3.4	1.7
9	3.5	1.6
10	4.4	2.2
11	4.5	11.6
12	5	2.5
13	7.3	4.9
14	7.4	8.5
15	9	11.7
16	10	5.7
17	11	4.3
18	11	5.1
19	11.7	5.1
20	16	12
21	23	34
22	29	9.9
23	33.2	8.6

Functionally, the icteric phase resembles extrahepatic incomplete biliary obstruction. Liver biopsies taken during this phase have presented three histologic features:[11, 12, 13, 14, 15, 16, 17, 18]

1. Bile stasis, predominantly in the central zone of the lobule, manifested by bile plugs in the canaliculi, bile-pigmented protein coagulates in neighboring liver cells, and bile-pigmented granules in Kupffer's cells. Some liver cells show rarefaction of cytoplasm (feathery degeneration). Where liver cells have disappeared in the centrolobular zone, mononuclear cells have accumulated.

2. Infiltration of edematous portal tracts with lymphocytes, histiocytes and segmented leukocytes, many of which are eosinophilic.

3. Focal necrosis of liver cells, with replacement by mononuclear cells.

The most conspicuous feature is bile stasis. Liver cell damage, if present, is relatively mild. It is frequently the result of cholestasis if feathery degeneration is seen. Portal tract inflammation is transient, tending to diminish and disappear as jaundice wears on.

Electronmicroscopic studies show alterations of the hepatic cell mem-

brane which lines the bile canaliculus. Normally, this membrane is thrown into regular folds, termed "microvilli." In jaundice due to chorpromazine, the microvilli either are absent from long stretches of the canaliculi, or are irregular, shortened, thickened and stunted.[15]

Sometimes, although administration of chlorpromazine has been stopped because of jaundice, jaundice has continued to increase for as long as four weeks afterward (table 5, cases 1, 2, 3).

Hepatic dysfunction usually disappears within weeks or months after chlorpromazine has been discontinued. However, jaundice or anicteric dysfunction may persist for more than a year (table 2, case 2).[13, 19]

In two quite similar cases (one of them ours), one, and one and one-half years after apparent clinical recovery, increased bromsulfalein retention, serum transaminase, serum alkaline phosphatase and total cholesterol still persisted.[20] In our own case, 15 months after jaundice had subsided, bromsulfalein retention was 19%; SGP-T, 104 units; alkaline phosphatase, 29 Bodansky units; cholesterol, 460 mg.; esterification ratio, 65%. Cephalin flocculation, thymol turbidity, zinc turbidity, total protein, A/G ratio and prothrombin time were normal.

Needle biopsies of the livers in these cases, studied by routine histologic methods, failed to throw any light on what these abnormalities might signify. In one, the liver appeared to be normal except for one small portion showing minimal inflammation in the portal region and adjacent binucleate cells, suggesting a slight degree of residual inflammation. In our case, three liver biopsies, obtained singly at intervals of six months, appeared to be normal.

Discussion

Pathogenesis of Hepatic Dysfunction Due to Chlorpromazine: During the initial month of daily chlorpromazine therapy, asymptomatic anicteric hepatic dysfunction may develop in as much as 50% of a group of patients. Dysfunction first appears four to 27 days after daily administration of the drug has been started. It is manifested by derangement of the hepatic cells, as reflected by increased bromsulfalein retention and serum transaminase. The latter is believed to result from acute liver cell injury.[21]

While drug administration is uninterruptedly maintained, hepatic dysfunction spontaneously subsides completely in almost all cases;[2] but in 1 to 2% it progresses to frank jaundice.[18]

After jaundice has appeared, the results of liver function tests resemble those found in extrahepatic, incomplete obstructive jaundice. Liver biopsies during this phase, studied by routine histologic methods, show intrahepatic cholestasis; an early inflammatory component, including eosinophilia, in the portal spaces; and little evidence of parenchymal injury. Electronmicroscopic studies of liver biopsies during the icteric phase disclose that the microvilli of all the bile canaliculi are absent for long stretches, or are irregular, shortened, thickened and stunted. It has been suggested that these altera-

tions of this specialized portion of the wall of the liver cell may be a primary lesion of this hepatic disorder.[15, 16] The cytoplasm of the liver cell appears to be uninvolved or only secondarily so, with inconstant and irregular alterations of the endoplasmic reticulum.[15, 16] The presence of bile precipitates and plugs within the canaliculi, it has been suggested, may possibly be due to a loss of function of the altered canalicular membrane, with resultant abnormal reabsorption of liquids or passage of material (perhaps protein or glycoprotein) into the bile favoring precipitation.[15, 17] Altered microvilli with intrahepatic cholestasis have been induced by other drugs in the absence of an inflammatory component, suggesting that these processes are independent of one another.[17, 18]

It remains for further investigation to determine if the ductules, also lined by microvilli, are likewise involved in this disorder.

There has not as yet been a sufficient period of observation of patients with prolonged, incomplete hepatic recovery from jaundice due to chlorpromazine to be able to state that the derangement induced by the drug always is ultimately wholly reversible.

Evidence for an Allergic Reaction: The mustered evidence suggests that this hepatic disorder is based upon an immunologic mechanism. Of the previously listed criteria for an allergic reaction, the following are considered to be fulfilled: immunizing event, latent period, accelerated reproduction of reaction following re-administration of a small dose of drug, specificity and desensitization. The presence of acquired antibodies has not been demonstrated.

After the first internal contact with chlorpromazine, there is a latent period of four to 27 days. This presumed incubation period of active sensitization to the drug or a metabolic product is followed by clinical manifestations of hepatic dysfunction. The incidence, time of onset and severity of dysfunction are unrelated to age, sex, size of the daily or total dose, or length of drug administration preceding onset.[2, 18, 35] The cumulative incidence of dysfunction increases during the initial three weeks of daily exposure to the drug (93%), then falls off sharply during the fourth week (table 1).

Although dysfunction and associated symptoms usually begin to subside rather promptly upon withdrawal of the drug, this does not always occur. In one case, 16 days after chlorpromazine had been withdrawn because of the development of gastrointestinal symptoms, these symptoms still persisted and frank jaundice first became apparent.[19] In other cases, for as long as four weeks after the drug had been withdrawn because hepatic dysfunction occurred, jaundice steadily deepened (table 5). In such instances, it is conjectured, chlorpromazine or a metabolic product may remain within the body tissues, providing an adequate antigenic stimulus for continuing antibody production and antigen-antibody reaction to elicit or intensify hepatic dysfunction.

The hepatic reaction is specific. Patients recovered from a bout of jaundice due to chlorpromazine do not thereafter react nonspecifically to any similar drug known to have a tendency to cause liver damage such as mepazine, prochlorperazine and promazine.

Rarely, cross-reactivity has occurred between chlorpromazine and promazine, a phenothiazine derivative differing from chlorpromazine only in lacking a chlorine radical.[24, 25]

Three weeks to 40 months after chlorpromazine had been discontinued in 17 patients, almost solely because of icteric or symptomatic anicteric hepatic dysfunction, re-ingestion of the drug provoked a recurrence or exacerbation of dysfunction in 13 patients within 24 to 48 hours, an incidence of 76%. In another group, nine of 14 patients developed positive hepatic responses to chlorpromazine challenge, an incidence of 64%.[35] Maximal dysfunction occurred 24 to 72 hours after the challenge had been started.

In two reported cases, hepatic dysfunction was demonstrated five and 15 hours after challenge.[26, 27] Gastrointestinal symptoms and fever sometimes occurred five to 10 hours after the first challenging dose had been administered, even when given as long as three years after the last previous dose of chlorpromazine.

Generally, the larger the challenging dose, the more intense the reaction. Anicteric dysfunction usually is provoked by a single dose of 25 mg. or less, and jaundice by a daily dose of 100 mg. or more.[8] Sometimes, however, jaundice has been provoked by a challenging dose of less than 25 mg.,[22] and anicteric dysfunction by a dose larger than 100 mg.[8]

A sensitized individual, when exposed to a repeated challenge with a fixed dose, may respond with an episode of accelerated hepatic dysfunction either equal to or—more usually—milder in intensity than its predecessor.

Hepatic desensitization to chlorpromazine has been demonstrated. Thirty-four of 68 patients developed asymptomatic hepatic dysfunction during their first month of chlorpromazine therapy.[2] In all of these, and in a few reported cases of jaundice, normal liver function returned while the drug was deliberately continued.[2, 28, 29] In two other groups of patients, after chlorpromazine had been discontinued because of drug-induced jaundice, its re-administration—following hepatic recovery—did not provoke recurrent hepatic dysfunction in 24 and 36%.[35] Occasionally, hypersensitivity to the drug has been lost after positive hepatic response to one or two challenges.[27] In these patients, it is conjectured, spontaneous desensitization may have occurred. Parallel phenomena have been observed in the behavior of allergic reactions caused by sulfonamides and penicillin.[30]

Deliberate hepatic desensitization to chlorpromazine was attempted in 10 patients and was successfully achieved in all. All exhibited persistence of hepatic hypersensitivity right into the early phase of desensitization. At the time of this report, chlorpromazine has been administered to all of them for periods ranging from two and one-half months to three years, the daily

dosages equaling or exceeding those administered before the original bouts of dysfunction.

If the drug is discontinued after desensitization to a small daily dose has been achieved for only a few weeks, the acquired tolerance to that dose may be lost within five weeks. If, however, a large dose is maintained daily for months and then discontinued, acquired tolerance to that dose is much longer lasting.

Based upon our experiences with deliberate desensitization, the following method is suggested. It should not be attempted until hepatic function has returned completely to normal, or has settled to a persisting plateau consisting only of slightly elevated bromsulfalein retention (about 7%), with or without slightly increased serum alkaline phosphatase (about 5 Bodansky units). An elevated serum transaminase forecasts failure of the attempt at desensitization. A positive cephalin flocculation can be ignored.

A single challenging dose of chlorpromazine (25 mg.) is administered at three separate intervals, two weeks apart. Two weeks after the third challenge, 25 mg. daily are administered for two weeks. Throughout this period, at two-week intervals, just before the next exposure to chlorpromazine is due, bromsulfalein retention and serum transaminase should be determined. If the results are within normal limits, or if the abnormal degree of dye retention is essentially like that preceding the first challenge, chlorpromazine may again be administered. If fresh abnormalities of dysfunction are present, however, chlorpromazine should be withheld; and, at intervals of one week, hepatic function should be reëvaluated until the results permit proceeding.

After chlorpromazine, 25 mg., has been administered daily for two weeks and hepatic function is found to be satisfactory, 50 mg. daily are then administered for one week. Subsequently, at intervals of three days, the following increments to the daily dosage are made: 25 mg., until 100 mg. daily; 50 mg., until 200 mg. daily; 100 mg., until 400 mg. daily; and increments of 200 mg. thereafter until the desired daily dosage is attained.

During this period of increasing dosage, bromsulfalein retention and serum transaminase should be determined weekly just before the next increment is due. If hepatic function is satisfactory, the increment may be given. If, however, fresh abnormalities of function are present, the increment should be postponed until they have subsided.

After the desired daily dosage has been achieved, it should be continued for a minimum of several months. Otherwise, omission of the drug for one month or longer might result in a deterioration of hepatic tolerance to that dosage. An exacerbation of dysfunction might then ensue upon readministration of the drug.

This suggested technic of desensitization might be accelerated by prophylactic use of large doses of corticosteroids for short periods to minimize and curtail hepatic reactions to small challenging doses of chlorpromazine. Also,

by performing liver function tests more frequently than recommended, one might be able to proceed faster with the progressive administration of chlorpromazine. These possibilities await investigation.

Thus far, skin tests of patients during or after an attack of jaundice have been negative. Patch tests with chlorpromazine produced no reaction in 48 hours. Intradermal injections of chlorpromazine or serum from patients ingesting large daily doses of the drug produced no reaction during the first hour and at 24 hours. By the technic of Prausnitz-Küstner, with the use as antigen of the sera from patients ingesting large amounts of chlorpromazine, intradermal tests were negative during the first hour and at 24 hours.

Adrenocortical Hormone: How adrenocortical hormones operate in allergic states is debatable. They probably have a peripheral effect on small arterioles and capillaries, in which the latter become impermeable to inflammatory elements. They also have the capacity, in very large amounts, to depress antibody synthesis to a small extent. They do not inhibit union of antigen and antibody.

The half-life of antibody protein is approximately 14 days.[30, 31, 32, 33, 34]

The data already presented indicate that the hepatic response to a small challenging dose of chlorpromazine can be partly inhibited by large prophylactic doses of synthetic adrenocortical hormone. Hepatocellular reactivity, as reflected by serum transaminase levels, can be depressed; but the reactivity as reflected by bromsulfalein retention seems little affected. Hepatic reactivity, as reflected by serum alkaline phosphatase, can also be depressed. The occasional appearance of a positive cephalin flocculation after a challenging dose is not affected by the prophylactic administration of synthetic adrenocortical hormone.

It is conjectured that this partial inhibition may result from hormonal depression of antibody synthesis which, in turn, diminishes the intensity of antigen-antibody reaction, thus lessening the degree of reactive injury of the biliary microvilli.

In established hepatic dysfunction due to chlorpromazine, the therapeutic administration of large doses of synthetic adrenocortical hormone fails to alter the natural course of the reaction. Others, too, have found corticosteroid therapy disappointing.[13, 22, 23] Underlying this failure, it is conjectured, may be the inability of the hormone to interfere with continuing union of antigen and antibody. It is further conjectured, from this failure, that the hormone does not directly suppress hepatic tissue reactivity.

Several types of allergic reactions producing tissue damage are recognized today: (1) direct effect of allergen and antibody on cell, as in allergic (true) purpura; (2) anaphylaxis; (3) Arthus' reaction; (4) delayed hypersensitivity. The present incomplete data on the development of chlorpromazine-induced jaundice do not permit classifying this reaction.

Further investigations along the following lines are suggested: identi-

fication or measurement of serum antibody or skin sensitivity to the allergen, with or without the use of liver cells or viable leukocytes; complement titer; serial histologic studies (routine and electronmicroscopic) of liver tissue during anicteric and icteric phases of hepatic dysfunction provoked by challenges with varying amounts of chlorpromazine, with and without the use of large prophylactic doses of corticosteroid, and correlation of the histologic findings with hepatic function tests.

Summary and Conclusions

In the development of hepatic dysfunction due to chlorpromazine, though the presence of circulating antibody could not be demonstrated by skin tests, the following criteria for an allergic reaction are considered to be fulfilled: immunizing event, latent period, accelerated reproduction of reaction upon reëxposure to a small challenging dose, specificity, and deliberate desensitization.

The onset of this hepatic disorder is characterized by hepatocellular derangement, manifested by increased bromsulfalein retention and serum transaminase.

Large doses of synthetic adrenocortical hormone, therapeutically administered after jaundice has been established, fail to alter the natural course of the disorder. Large doses of the hormone, prophylactically administered, partially inhibit hepatic response to a small challenging dose of chlorpromazine. It is suggested that the prophylactic effect of the hormone is due to depression of antibody synthesis, and the lack of therapeutic effect to its inability to prevent union of antigen and antibody.

Deliberate hepatic desensitization to chlorpromazine has been successfully achieved in 10 cases. Large daily doses have been continued as long as three years without adverse effect upon the liver. A method of deliberate desensitization has been described.

Areas for further investigation have been suggested.

Acknowledgment

I am indebted to Dr. Bernard Davis and Dr. Byron Waksman, of Harvard Medical School, and to Dr. Norman Zamcheck, of Mallory Institute of Pathology, for their helpful critical suggestions in the preparation of this report.

Summario in Interlingua

Durante le prime menses del administration diurne de chlorpromazina, anicteric dysfunction hepatic pote disveloppar se in usque a 50% del patientes in un gruppo particular. Le declaration del condition es manifeste in disrangiamento hepatocellular, reflectite in augmentos del retention de bromsulfaleina e del nivello seral de transaminase. In quasi omne le casos, le dysfunction subside in le curso de un continue, non interrumpite administration del droga. In 1 o 2%, illo progrede usque a jalnessa patente.

In le disveloppamento de dysfunction hepatic como effecto de chlorpromazina—ben que le presentia de anticorpore circulante non poteva esser demonstrate per tests

cutanee—le datos clinic pareva satisfacer le criterios de un reaction allergic: Evento de immunisation, periodo de latentia, reproduction accelerate del reaction post re-exposition a un micre dose de provocation, specificitate, e dissensibilisation planate.

Tres septimanas a 40 menses post le suspension de chlorpromazina in 17 patientes a causa de icteric o symptomatic anicteric dysfunction hepatic, le re-ingestion del droga provocava un recurrentia del dysfunction in 13 intra un periodo de inter 24 e 48 horas Isto es un incidentia de 76%.

In 10 casos, un planate dissensibilisation a chlorpromazina esseva essayate. In omnes a bon successo. Le uso del droga ha essite continuate durante periodos de usque a tres annos sin effecto adverse in le hepate, con doses diurne equal o superior a illos administrate ante le episodio original de dysfunction.

Es describite un methodo de dissensibilisation planate.

Grande doses de synthetic hormon adrenocortical, administrate prophylacticamente, inhibi partialmente le responsa hepatic a micre doses provocatori de chlorpromazina. Grande doses del hormon, administrate therapeuticamente post que le jalnessa es establite, non altera le curso natural del disordine. Es suggerite que le effecto prophylactic del hormon resulta de un depression del synthese de anticorpore, durante que le absentia de un effecto therapeutic del droga pare significar que illo non es capace a prevenir le union de antigeno e anticorpore.

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PERMANENT CONTROL OF NOSEBLEEDS IN PATIENTS WITH HEREDITARY HEMORRHAGIC TELANGIECTASIA *

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RECURRENT familial epistaxis was first recognized by Babbington [1] in 1865. He reported "hereditary epistaxis" in five generations of a family. Legg in 1876 [2] confused the disorder with hemophilia, as did Chiari in 1887 [3] and Chauffard in 1896.[4] Rendu [5] distinguished it from hemophilia in 1896. Meanwhile Osler,[6] at The Johns Hopkins Hospital, had been observing three patients with the disorder, and in 1901 published his classic description, "On a Family Form of Recurring Epistaxis with Multiple Telangiectases of the Skin and Mucous Membranes."

After Osler's account, Kelly in 1906 [7] presented excellent color drawings of patients with multiple telangiectases. Weber [9] described a family in 1907, and Hanes [10] suggested the name "hereditary hemorrhagic telangiectasia" in 1909. The condition is also commonly known as Rendu-Osler-Weber disease.

GENETICS

The disorder is transmitted as a simple dominant trait. It affects either sex. Children have a 50% chance of inheriting the disease if only one parent is affected. Snyder and Doan [11] reported a family in which both parents were affected. Their infant was born with multiple telangiectasia, rapidly developed other lesions, and died at 11 weeks of age. The report suggests that the gene for multiple telangiectasia is lethal when homozygous.

Although it is called hereditary, not all patients with this disorder have a positive familial history. In fact, one of Osler's patients did not. F. Parkes Weber [12] says: ". . . the diagnosis of telangiectasia of the Osler type can (though rarely) be made in the absence of any family history. In such cases either the information about the family history must be defective or else the patient must be regarded as the first in the family to manifest the condition (a gene mutation)." Two of the patients presented in this paper, although undoubtedly examples of "telangiectasia of the Osler type," have no family history of the disorder.

PATHOLOGY

The microscopic pathology has been described many times. It is generally recognized as a congenital defect in the development of the terminal

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loops of the capillaries. As early as 1909 Hanes,[10] in an excellent article, said: "A study of sections stained by various special methods failed to reveal any muscular or elastic tissue in the walls of the dilated superficial vessels. The disease has been referred to as a hemorrhagic diathesis—a term which not only covers all the symptoms, but conceals most of them." In 1956 Livingston and Carr [13] further described the pathology: "Microscopic study demonstrates vascular sinuses of irregular size and shape, lined by a thin layer of endothelium. Muscular and elastic coats are absent. Because of the thin walls and proximity to the surface, these sinuses bleed readily with slight trauma and, because of lack of contractile elements in the wall, bleeding may not cease spontaneously. They are sinuses interposed between arteries and veins."

Symptoms

Epistaxis is by all odds the most common and usually the most troublesome symptom in patients with hereditary hemorrhagic telangiectasia. However, the same telangiectases found in the nasal mucosa have been reported in virtually every organ and on every body surface. Osler was aware of lesions in the gastrointestinal tract. Hereditary hemorrhagic telangiectasia is well recognized as a cause of spontaneous hemothorax. In addition, rare instances of bleeding into the liver, spleen, meninges, kidney and larynx have been reported.

Gastrointestinal bleeding is probably next in frequency after nosebleed. In some patients, mucous membrane lesions on the lips, tongue and gums (which are common) also bleed occasionally. Skin lesions, particularly about the cheeks, ears, nose and fingertips, are almost always present but rarely bleed. There is a tendency for new telangiectases to appear as the patient grows older.

Most lesions are slightly elevated and bright red. They blanch with pressure. On the cheeks the lesions often look like spider nevi.

The Nosebleeds of Hereditary Hemorrhagic Telangiectasia

In hereditary hemorrhagic telangiectasia, nosebleed, beginning about puberty, is the cardinal symptom. Epistaxis may recur daily, or sometimes only a few times each year. Often there are frequent minor hemorrhages, unpredictable and annoying, and then a serious hemorrhage two or three times a year. Many patients are unable to maintain hemoglobin values of even 10 gm. for any period of time. Many have been hospitalized at one time or another for blood transfusions.

Here is an excerpt from Osler's account of a patient with a typical nosebleed. He is describing a 49 year old man who had had nosebleed most of his life.

"When 10 years old the patient began to have epistaxis which often followed the trick of walking on his hands. He would bleed quite profusely for part of a day,

or for some hours every day for 10 days or more, until he got quite weak and anemic.

"In the first 10 days in the hospital there were six bleedings from the nose. Cauterization of the angiomata on the septum was followed by quite profuse hemorrhage, which was readily stopped. The next day the hemorrhage recurred and he lost 580 c.c. of blood before it was checked by plugging. Half an hour later he had a second hemorrhage in which 820 c.c. were lost. He said he frequently had much more profuse hemorrhage."

Osler quoted another of his patients as remarking "with quiet good humor" that because of nosebleeds "he was in the habit of bleeding to death every day."

Older Treatments

In the past, treatment of epistaxis in patients with hereditary hemorrhagic telangiectasia has been notoriously ineffective. Such medications as moccasin venom, rutin, vitamin K, ascorbic acid and estrogens have been used, with indifferent results. Surgical measures such as arterial ligation, the submucous resection operation, nasal packing, and chemical or electrical cautery have never provided permanent benefit. One of my patients, an old man, said that after 300 he gave up counting the number of times his nose had been cauterized and packed. A woman who was using estrogens said she thought her medication helped because now she used only 500 cotton balls (for plugging) every six months, as compared to a greater number previously.

Many physicians feel that the less done to the nasal mucosa, the better. One of Osler's patients, who wrote to him in 1898, seems to have agreed: "I am still troubled with the hemorrhages, but am able to attend to business. I have procured in the last three months a gum arrangement which I insert and inflate with air, and keep it in for 15 or 25 minutes, and it stops the bleeding entirely. It is a great improvement on the old plan of plugging with cotton or anything else."

Septal Dermoplasty

At the October, 1959, meeting of the American Academy of Ophthalmology and Otolaryngology in Chicago, I presented a paper [14] and a motion picture describing an operation called "septal dermoplasty," for the permanent control of nosebleeds caused by hereditary hemorrhagic telangiectasia. The exact surgical technic was described.

Principles: Septal dermoplasty for the permanent control of severe nosebleed in patients with hereditary hemorrhagic telangiectasia is based on the following principles:

First, the cause of most anterior nosebleeds, including hereditary hemorrhagic telangiectasia, is *trauma.* The mucosa of the anterior third of the nasal septum is injured by drying, picking, sneezing or similar minor trauma, and it bleeds. Of course, in hereditary hemorrhagic telangiectasia lesions

are present in all parts of the nose, not just on the septum. But except for an occasional nosebleed, usually from the anterior end of the inferior turbinate, only the anterior part of the nasal septum bleeds in this disorder.

Second, skin, being much tougher than nasal mucosa, when grafted onto the anterior third of the septum will withstand any type of ordinary trauma without bleeding. The excellent blood supply of the septum assures a complete take of the graft.

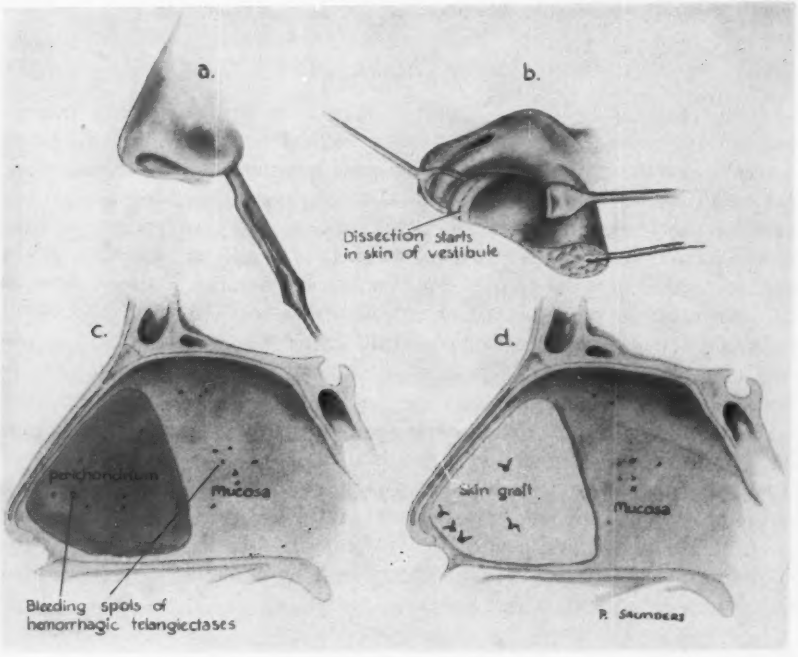


FIG. 1. (a) This incision makes work on the septum easier. (b) Second incision begins in skin of vestibule. (c) Only mucosa is removed; perichondrium is left. (d) The skin graft in place. A similar graft is placed on other side.

Thus, septal dermoplasty is effective in controlling the nosebleeds of hereditary hemorrhagic telangiectasia because, in this operation, *the fragile mucosa of the anterior part of the nasal septum is replaced by tougher skin.* It is the substitution of skin for mucosa that prevents the nosebleeds, not the mere removal of mucosa-containing telangiectases.

The Technic (Figure 1 *a, b, c, d*)*:* The technic is described fully in a forthcoming issue of the *Transactions of the American Academy of Ophthalmology and Otolaryngology.*[14] A motion picture is also available showing the technic in detail. Briefly, however, a split-thickness skin graft is removed from the thigh or buttock under local anesthesia. After excision of

septal mucosa, the graft is fixed to the anterior third of both sides of the nasal septum. The graft extends from *dorsum to floor* of the nose, and comes far enough anteriorly to be sutured to vestibular skin. Posteriorly it extends about one third of the length of the septum.

Nasal packing is left in place for four days. Postoperatively, there is crusting for three or four weeks. Then the grafted area usually ceases to crust or, if any minimal crusting persists, it is easily controlled by application of mineral oil or an ointment such as Cortisporin.

Results: Eight patients with severe epistaxis caused by hereditary hemorrhagic telangiectasia have been operated upon in the last year. Several had suffered daily nosebleeds for years. The hemoglobin values, preoperatively, ranged from 3.7 gm. to 8 gm. Since operation, no patient has bled severely. Some have bled a little from telangiectases on the anterior end of the inferior turbinate. Telangiectases further back in the nose have not bled because they are not traumatized.

All eight patients, after transfusions and septal dermoplasty, have been able to maintain their hemoglobin values at normal levels for the first time in years.

Summary

Hereditary hemorrhagic telangiectasia is a cause of severe recurrent nosebleeds. Septal dermoplasty is a new surgical procedure that controls these nosebleeds permanently.

Summario in Interlingua

Hereditari telangiectasia hemorrhagic es un disordine que causa frequente e sever epistaxis. Hemorrhagias occurre occasionalmente ab altere sitos (per exemplo le vias gastrointestinal), sed il es le sanguination nasal que rende le majoritate de iste patientes chronicamente anemic e mesmo debilitate. Le epistaxis comencia in le etate pubere e continua usque al fin del vita. In le caso typic, le patiente experientia un sanguination de alicun guttas per die, usque—post un o duo septimanas—un hemorrhagia de tal grados de severitate occurre que possibilemente un transfusion de sanguine deveni necessari.

In le passato, omne effortio medical o chirurgic de dominar iste sanguinationes nasal ha remanite van. Sed nunc—per medio de un nove technica chirurgic que nos designa como dermoplastia septal—il es possibile curar le epistaxis de patientes con hereditari telangiectasia hemorrhagic. In tal patientes il es le tertio anterior del septo nasal que produce le plus extense sanguinationes. De facto, in altere areas del naso, le occurrentia de un hemorrhagia es multo improbabile a causa del improbabilitate de lor traumatisation. Pelle obtenite ab le gamba es graffate a in le naso de maniera que illo coperi le tertio anterior del septo nasal. Iste nove epithelio es forte e capace a resister a traumatisation. In 15 patientes tractate per iste methodo le resultatos esseva excellente.

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DILATATION OF THE COLON, A SERIOUS COMPLICATION OF ULCERATIVE COLITIS *

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In the natural course of ulcerative colitis, serious colonic complications may be expected in from 5 to 10% of the cases.[1] These have consisted of free perforation, pericolonic abscess, peritonitis, massive hemorrhage and carcinoma. Not previously included in this group is a rapidly developing and striking dilatation of the colon associated with extreme toxicity. The abdomen becomes distended and usually silent. Though potentially reversible, this ominous sign markedly increases the likelihood that a perforation has occurred.

Single examples of this entity were first described by Marshak et al.[2] as "megacolon, a complication of ulcerative colitis," and by Madison and Bargen [3] as "fulminating chronic ulcerative colitis with unusual segmental dilatation of the colon." A comprehensive study by Lumb et al.[4] stressed the pathologic aspects, characterized by the inflammatory process rapidly involving all coats of the colonic wall. The term "toxic aganglionic megacolon" was used by Bockus et al.[5] to describe the dilatation, which they suggested was caused by destructive changes in the nerve plexus of the colon, especially the myenteric plexus. They observed that the distended colons in some instances had for many years previously shown the x-ray appearance of marked narrowing and fibrosis.

Since most reported cases of toxic dilatation of the colon have been observed since 1950, it is tempting to correlate its occurrence with the introduction of ACTH and adrenal steroids to the treatment of ulcerative colitis. We have observed the entity 19 times in 16 patients at The Mount Sinai Hospital, all except one during the years 1954 to 1958, and the clinical course has been detailed.

The following are representative cases.

Case Reports

Case 1. A 45 year old female with a four-year history of ulcerative colitis was admitted to The Mount Sinai Hospital with a febrile, toxic exacerbation of her disease. The abdomen was soft, with left lower quadrant tenderness but no rebound tenderness. A barium enema examination showed the changes of ulcerative colitis from the splenic flexure to the rectum, with moderate dilatation of the sigmoid (figure 1A). On the fourth day the patient was started on prednisone. On the

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FIG. 1. A. *Case 1.* Barium enema examination shows changes of ulcerative colitis from splenic flexure to rectum. The sigmoid is moderately dilated. B. *Case 1.* A simple roentgenogram of the abdomen, taken three days after barium enema study, shows huge distention of the transverse colon, without increase in length, and increased distention of the sigmoid. The "cobblestone" appearance of the residual barium in the transverse colon is consistent with the presence of diffuse ulceration.

following morning the abdomen became progressively distended, and no bowel sounds were heard. The patient was treated with intravenous fluids and antibiotics, and the prednisone was stopped. The abdomen, however, remained distended, and a plain x-ray of the abdomen showed that the transverse colon was hugely dilated and the distention of the sigmoid had increased (figure 1B). Tenderness was now diffuse, with slight rebound. Because a perforation was suspected, a tube cecostomy was performed. The exploration revealed extreme distention of the transverse colon, splenic flexure and small bowel. Though the postoperative course was stormy, the patient gradually improved, and there has been no recurrence.

Case 2. A 24 year old male was admitted to the Mount Sinai Hospital with a 14-month history of ulcerative colitis, now complicated by arthritis of the knee joint and erythema nodosum. He was treated with ACTH gel, which resulted in cessation of fever but continuation of bloody, loose fecal discharges and cramps. After eight days of treatment he complained of right lower quadrant pain, and evidence of peritoneal irritation was noted. Because a perforation was suspected, the ACTH was stopped. On conservative management the patient improved symptomatically, but the temperature rose and the abdomen became progressively distended and tympanitic. An x-ray of the abdomen revealed marked dilatation of the cecum and of the ascending and transverse colons (figure 2). At surgical exploration there was free air in the peritoneal cavity, but no gross peritonitis. In the sigmoid area a deep ulcer went through to the abdominal wall. There were extensive edema and thickening of the peritoneum over the bowel, which was red and angry, and distended to three times normal size. The transverse colon was also adherent to the abdominal wall, with a thick strip of fibrin running across this area. An ileostomy and a subtotal colectomy were performed, the specimen revealing deep ulcers corresponding to the sites of perforation, and fresh filmy exudate and fibrous adhesions throughout. The postoperative course was stormy, and required multiple secondary surgical procedures, but the patient finally improved and has been well since.

Case 11. A 32 year old female with known ulcerative colitis for 10 years was admitted to The Mount Sinai Hospital with fever and bloody fecal discharges. She had been treated with ACTH prior to admission. The abdomen was moderately distended, with diffuse tenderness, absent bowel sounds and rebound tenderness in the left lower quadrant. An x-ray of the abdomen revealed a dilated colon.

The patient was treated by Cantor tube attached to suction, intravenous hydrocortisone and antibiotics. After five days she was afebrile, and the abdomen was minimally distended and without tenderness or rigidity. She was discharged on maintenance steroid therapy, and a year later was still asymptomatic.

Case 16. This 62 year old male with ulcerative colitis of two months' duration was admitted to The Mount Sinai Hospital with weight loss, fever and diarrhea. The abdomen was protuberant, soft and doughy. He was treated with oral antibiotics, without success. Tenderness and rebound tenderness developed in the left lower quadrant, and a flat plate of the abdomen revealed a colon with ragged margins, outlined with air. The dilatation was particularly prominent in the distal transverse colon.

After 12 days the abdomen was markedly distended, and the blood pressure had fallen to 96/60 mm. of Hg. Surgical intervention was advised, but the patient was started on ACTH. The improvement was dramatic, and when it had been maintained for a week, ACTH was stopped. He was discharged asymptomatic.

Clinical Features

The striking dilatation of the colon may occur either early or late in the course of ulcerative colitis, but in 13 out of 16 patients it complicated an acute

exacerbation of the disease. The colonic distention becomes evident only after toxic symptoms have been present for from two to eight weeks. In all of these patients it was the manifestation of a marked increase in the severity of the underlying disease.

All patients were febrile, toxic and dehydrated. Most had tachycardia, anemia, hypotension, and moderate to severe depression. The white blood count was increased in all but three, and toxic granulations were noted in these three, as well as in most of the others. The abdomen was distended



FIG. 2. *Case 2.* A simple roentgenogram of the abdomen shows distention of the ascending and transverse colon and of the sigmoid. The rectum is filled with air but remains limited in distensibility.

and tender, and rebound tenderness was present in seven patients. The abdomen was often soft or doughy, rather than rigid, except in the areas of tenderness. Tympany was usually present, and the bowel sounds were hypoactive or absent. In a few instances there was moderate to massive rectal bleeding, without fecal discharge, just prior to or coincident with the distention. In nine patients the distention and the abdominal tenderness suggested that a perforation of the colon had occurred; six of these patients were explored surgically, and a perforation was found in four. In the remaining patients it was felt that a perforation was impending but had not yet occurred. In two who were explored surgically, and in another examined post mortem, no perforation was found.

Radiologic Features

The x-ray finding of a markedly dilated colon in association with severe ulcerative colitis is usually pathognomonic. The radiologic features, unassociated with the clinical picture, must be differentiated in some cases from paralytic ileus, colonic obstruction, sentinel dilatation in acute pancreatitis, dilatation of small bowel loops in ileojejunitis, and the marked colonic dilatation occasionally seen in sprue. Most characteristic of the true toxic dilatation of the colon in ulcerative colitis is the remarkable localization to colonic segments, particularly the transverse colon, in association with evidence of severe intrinsic inflammatory disease of the colonic wall. Often the deeply penetrating ulcers will be outlined by the air contrast. The rectum seems never to be involved.

A review of barium enema x-ray examinations in these patients prior to the onset of dilatation revealed that the deep undermining ulcers were present in almost all cases. The antecedent colitis was usually universal.

The value of the flat plate of the abdomen in the course of febrile ulcerative colitis with increasing abdominal pain is well documented by the present study.

Pathologic Features

The eight resected colons and the one examined post mortem were characterized by severe ulcerative colitis extending through to the muscularis. Though true perforation was present in only four, all were involved with multiple ragged ulcerations. One perforation was sealed off by thin, tenuous omental adhesions, while the other three were complicated by pneumoperitoneum. Of the latter three, there was partial walling off in two, one with and one without purulent peritoneal fluid. The third had diffuse peritonitis with no evidence of walling off. Three perforations occurred at the splenic flexure or at the distal transverse colon, while in the fourth patient there were three distinct perforations (transverse, sigmoid and cecum). In the areas of dilatation the bowel wall was usually thinned. In most cases the serosal surface was covered by thin, filmy adhesions.

The pathologic features of this phase of ulcerative colitis have been carefully studied by Lumb and his associates.[4] They have stressed the gross appearance of dilatation and thinning of the colonic wall, associated with ragged ulceration, and the microscopic involvement of all elements of the colon with striking inflammatory and reactive changes. Bockus et al.[5] have stressed the destruction of the ganglion cells, demonstrating complete absence of the ganglion structures in the submucosa and muscular layers of many sections, as well as degenerative changes in the nerve structures in other areas. The dilated colon of Hirschsprung differs from this entity in that it is normally innervated, and there is evidence of obstruction in the spastic denervated segment. There is no evidence of organic obstruction in the toxic dilatation of ulcerative colitis.

Etiologic Speculations

The most likely cause of the colonic distention is the marked inflammation of all coats of the colonic wall. Whether involvement of the ganglia is specifically responsible remains unclarified. Though hypopotassemia has been implicated as a cause in an instructive case reported by Cohn et al.[6] we have not been able to document this with our serum electrolyte studies or response to potassium therapy. In only one patient was the electrocardiogram consistent with hypopotassemia. The serum potassium was normal in all others when studied, with the exception of one with an elevated serum potassium. Though it is recognized that a normal serum potassium can mask a cellular potassium deficiency, a clear-cut improvement following administration of intravenous fluids containing potassium was not evident, even in the one patient with electrocardiographic evidence of hypopotassemia. When in some cases there was a favorable response, interpretation was complicated by other therapeutic maneuvers. The cause-and-effect relationship of a frequently found hypochloremia and a moderate hyponatremia is also to be determined. The marked depression of the serum albumin reflects the severity of the debilitating illness, and probably pathologic changes in the liver.

The one segment of involvement common to all cases was the transverse colon, and even when the process was diffuse it was usually most marked here. We might speculate that the lax mesentery of the transverse colon permits this segment and its contained gas to rise to the highest level in the supine as well as in the erect position. Furthermore, since deep involvement of the muscular coat results in hindered peristalsis, gas becomes trapped in its normal course between the two major colonic flexures. The toxicity commonly associated with severe ulcerative colitis is still more marked here, because of the thinning of the bowel wall caused by the gaseous distention. Though the toxic dilatation may occur in a previously fibrosed, narrowed segment of colon, the infrequency of involvement of the rectum itself is per-

haps best correlated with its being the segment of longest standing disease and scarring.

Prognosis

The serious prognosis for the patient with ulcerative colitis complicated by toxic dilatation of the colon is indicated by the mortality of 18.8% (three deaths). Two deaths occurred without surgery, and a third in the postoperative period. Of the 11 patients operated upon (table 1), the average period of hospitalization was three months, with a range of three weeks to

Table 1

Surgical Therapy

Case No.	Type	When Performed in Relation to Distention	Result	Perforation
1	*Cec.	3 days	Improved	
2	†Il-stc.	20 days	Improved	+
3	Il.-stc.	3 days	Improved	+
4	Il.-stc.	12 days	Improved	+
5	Il.-stc.	5 days	Improved	
6	Il.-stc.	‡2 months	Improved	
8	a) Il.	‡9 months	Not improved	
	b) Stc.	10 months	Improved	
9	a) Cec.	12 days	Improved	
	b) Il.-stc.	Effective		
10	Il.-stc.	1 day	Died	+
13	Il.-stc.	11 days	Improved	
15	Cec.	12 days	Improved	
11 Total				

* Cec.—cecostomy.
† Il.-stc.—ileostomy, subtotal colectomy.
‡ Performed after recurrent distention.

10 months. The stormy postoperative course of six patients accounted for the prolonged medical care and was contributed to by pulmonary emboli, metastatic infections and multiple secondary operative procedures. Nine patients were left with a permanent ileostomy.

Management

In all instances an attempt was made to manage this complication by medical measures: antibiotics, and correction of fluid and electrolyte deficits by intravenous replacement. Seven patients were also treated by long tube intubation, though in three only preoperatively.

Of the 16 patients, five improved on medical therapy, including two with intubation. All five had received steroids, four improving concomitantly with their administration, and one only when the steroids were withdrawn. Two ultimately required colectomy following recurrence of toxic dilatation, two and nine months later (table 1).

Eleven patients required surgical intervention. Seven were treated by

ileostomy and subtotal colectomy performed as an emergency measure. One patient died postoperatively, while the others improved. One patient treated by ileostomy alone did not improve until colectomy was performed one month later. Three other patients were treated with decompression of the colon by cecostomy. All improved, and one later had an elective colectomy.

The Role of ACTH and the Adrenal Cortical Steroid Hormones

The present series is heavily weighted by the number receiving these agents, in that only one patient (case 15, table 2) had received no hormonal therapy at any time. It is evident that ACTH and the adrenal steroids

Table 2

ACTH and Adrenal Steroids in Relation to Toxic Dilatation of Colon

Case No.	Previous Steroid Therapy	Steroid Therapy Immediately Prior to Admission	Steroid Therapy in Hospital	Relation of Distention to Steroids	Result
1	0	0	Prednisone	1 day after	Worse (S)
2	+	0	ACTH gel	8 days after	Worse (S)
3	+	+	0	—	Worse (S)
4	0	0	ACTH gel	9 days after	Worse (S)
5	+	+	0	—	Worse (S)
6	0	0	ACTH	†Before	‡Improved
7	+	+	I.V. hydrocortisone	Before	Died
8	+	+	ACTH	Before	‡Improved
9	+	0	ACTH, prednisone	†Before	Worse (S)
10	0	0	ACTH	6 days after	Worse (S)
11	+	+	*I.V. hydrocortisone	Before	Improved
12	+	0	*0	—	Improved
13	+	+	Triamcinolone	Before	Worse (S)
14	?	0	I.V. hydrocortisone	Before	Died
15	0	0	0	—	Worse (S)
16	0	0	ACTH gel	Before	Improved

* Treated by Cantor tube, antibiotics and intravenous fluids.
† Became much worse after steroids started.
‡ Exacerbation in two months and nine months respectively, associated with toxic dilatation and requiring surgical intervention.
(S) Surgical intervention.

cannot be held to be entirely responsible for the occurrence of toxic dilatation, since this entity was noted prior to the steroid era. Its increase in frequency or severity, however, can be grossly correlated, as is documented here. No previously reported cases mention the use of steroids.

Six patients received steroid therapy immediately prior to hospital admission (cases 3, 5, 7, 8, 11 and 13), and this was continued in four (cases 7, 8, 11 and 13). While two of the four improved, one became worse and required surgery, and the other died. Both patients whose steroids were stopped became worse and required surgery.

Of eight patients who received steroids after hospital admission, two improved dramatically, five became worse and required surgery, and one died.

Two patients (cases 13 and 15) received no steroids immediately prior to or during the hospital stay. One responded to conservative medical therapy, while the other became worse and required surgery.

Though it would be difficult to conclude from these data that the steroids had any unfavorable influence on the course of toxic dilatation, other observations have been more suggestive. In four patients (cases 1, 2, 4 and 10) the distention followed the onset of steroid therapy by from one to nine days, and three of these were among those cases where perforation was later demonstrated. Though again, accurate correlation as to the cause and effect cannot be made, it is important that in two other patients the distention already established became dramatically accentuated following steroid therapy (cases 6 and 9). In both there was improvement when the steroids were stopped, though this was only transient in one. In three other patients (cases 7, 13 and 14) where distention either preceded or seemed unrelated to the administration of steroids, the introduction of steroid therapy in the hospital resulted in either no improvement or worsening of the disease. Two of these three died before surgical intervention.

On the contrary, four patients improved dramatically, three (cases 6, 8 and 16) with ACTH and one with intravenous hydrocortisone.

Discussion

There is little doubt that distention of the colon in the course of ulcerative colitis is a serious prognostic sign. In this study, emergency surgical intervention was indicated in 69%, and the total mortality was 19%.

Though the operation of choice is ileostomy and colectomy in the treatment of ulcerative colitis, we have the definite impression that surgical decompression is preferable, at least as a primary procedure, when the colon is markedly dilated. When the ileocecal valve is incompetent, as is frequently the case in chronic ulcerative colitis, and the small bowel is dilated, as occurred in several of our patients, decompression by long tube intubation should be attempted. When this procedure is unsuccessful in relieving the distention, a simple cecostomy may be performed. The favorable response to cecostomy which occurred in three patients in this series is suggestive evidence of the usefulness of this measure. When colectomy is attempted and the colon is markedly inflamed and ulcerated, the surgeon often finds that, even with the most careful mobilization, the thin wall tears, resulting in gross peritoneal soiling. A successful cecostomy results in decompression and allows time for healing. In two of our cases, no further definitive surgery was necessary, while in the third, time was gained for a colectomy to be performed electively.

The decision as to when to intervene surgically in the presence of toxic dilatation is among the most difficult to make in the management of ulcerative colitis. There were two deaths in five patients who were not operated upon, and one death in 11 patients who were. In Bockus' series of seven patients,

four were operated upon and two died postoperatively; and in Lumb's series of seven patients, six patients were operated upon, with four deaths. In our series, seven patients had a prolonged and complicated postoperative course, contributed to by peritonitis and gross soiling. When perforation is expected, however, there appears to be little choice, in that surgery offers the patient with a perforated colon his only chance for improvement.

The problem of the therapeutic usefulness of ACTH and adrenal corticoids is also complex, and a dogmatic attitude is not justified at present. It has been confirmed that steroid therapy is of definite advantage in the severe exacerbation of ulcerative colitis. The ability of steroids to interfere with the healing process is also understood and feared when an impending perforation is suspected. The analysis of cases presented here conforms to the delicate balance expected between healing and furthering of perforation, in that eight patients became worse and four improved.

It would seem reasonable to formulate these general principles of management:

1. If toxic dilatation occurs when a patient is receiving steroids, these should be continued, intubation should be attempted, and, if unsuccessful, steroids should be maintained during and after surgery.
2. If a patient develops toxic dilatation when there is little doubt that a free perforation or even a large, walled-off perforation has occurred, it is apparent that steroids should be avoided. When it is likely that perforation has not yet occurred, steroids may effect dramatic improvement, but the precaution of small intestinal intubation and decompression should be taken concomitantly.
3. In a patient with acute, fulminating colitis whose barium enema reveals deep undermining ulcerations, steroids should not be started.

Summary

The rapid development of striking colonic distention is one of the most serious complications of ulcerative colitis, usually occurring during an acute exacerbation of the chronic disease. A study of 19 episodes in 16 patients is reported, with description of clinical, radiologic and pathologic features, as well as speculations on etiology. A simple x-ray film of the abdomen is usually diagnostic, and reveals marked colonic dilatation, most pronounced in the transverse colon and sparing the rectum. Deep ulcerations are seen by air contrast. Pathologically, involvement of all elements of the colon with inflammatory changes was striking. Perforation was demonstrated in four cases. There were three deaths, a mortality of 19%. Nine patients required emergency surgery. Six were treated by ileostomy and subtotal colectomy, with one postoperative death and three prolonged, stormy courses. Three were treated with decompressing cecostomy, all with improvement, and we emphasize that the results of this approach were so favorable as to demand further trial for these specific circumstances. Twelve patients were

treated with ACTH or adrenal steroids coincident with the colonic distention, and in some instances the beneficial or detrimental results were clearly evident. Recommendations for future management include the indications for ACTH, adrenal corticoids, long tube intubation and decompressing cecostomy.

Addendum

A review of records on patients with ulcerative colitis admitted to the Mt. Sinai Hospital between 1931 and 1950 reveals many additional instances of marked toxicity associated with abdominal distention. Most of these probably manifested colonic dilatation, as was confirmed by simple roentgenogram in some cases. This observation eliminates ACTH and adrenal steroids from primary responsibility for this serious complication. There is little doubt, however, that in some cases the introduction of these hormones will increase the likelihood of perforation and in other cases will reverse it. The result is probably influenced by the depth of ulceration, and this must often be evaluated on clinical grounds alone.

Summario in Interlingua

Le entitate del marcate distension del colon que occurre como complication del curso de colitis ulcerative es describite, e experientias colligite in 19 episodios in 16 patientes es reportate. Le frappante dilatation occurre usualmente durante un acute exacerbation del morbo chronic. Perforation del colon esseva trovate in quatro del patientes. Le serie includeva tres mortes. Un de istos esseva post-operatori.

Es sublineate le valor del roentgenogramma abdominal simple (sin substantia de contrasto) pro le precoce detection de distension colonic. Le dilatation es le plus pronunciate in le colon transverse, durante que le recto remane restricte. Examines post clyster a barium ha revelate que le antecedente colitis es usualmente de typo universal plus tosto que segmental, e in omne casos profunde ulcerationes colonic habeva occurrite con erosion subsuperficial. Istos es etiam visualisabile per contrasto a aere in pelliculas simple. Pathologicamente, a parte le ulceration, frappante affectiones esseva notate in omne le elementos del colon, incluse le stratos muscular, con inflammation e alterationes reactive.

Le exacte mechanismo responsabile pro le marcate distension colonic non es cognoscite, sed speculationes es presentate super le base de observationes clinic, radiologic, e pathologic. Le rolo de ACTH e del hormones steroidic adreno-cortical es evalutate. Le question de iste rolo es complexe, sed il pare haber indicationes pro le uso de ille agentes in certe casos e contra lor uso in alteres.

Dece-un del patientes requireva un intervention chirurgic. Tres de istes esseva tractate per cecostomia. Le responsa a iste forma de decompression chirurgic esseva si favorabile que on es inclinate a considerar lo como le technica de election in le chirurgia initial.

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HOMOLOGOUS SERUM HEPATITIS IN YOUTHFUL HEROIN USERS*

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The high incidence of homologous serum hepatitis among youthful drug addicts has been reported by other investigators.[1-7] Previous studies have been concerned with the epidemiology of serum jaundice and with the hospitalized patient in the acute stage of his illness. This report describes a study conducted over an 18-month period on an ambulatory group of 21 native-born white narcotic users in New York City, 16 to 23 years of age, exposed to a common source of needles. The prevalence of persistent hepatitis, relapse or reinfection in this group is described.

Material

An outbreak of jaundice had occurred in the spring of 1957 among a group of youthful narcotic users in the immediate neighborhood of The New York Hospital. Some of these patients were treated at the out-patient department clinics. These first patients, after their initial visit, were extremely helpful in enlarging the series. Forty-eight narcotic users were communicated with. Twenty-three presented themselves at the clinic, and only two later withdrew from the study. All of these patients were followed periodically whether or not they showed evidence of hepatic disturbance.

Methods

Questionnaire: At the initial interview, a check-list type of questionnaire was filled out for each patient. It gave information about severity, duration, and recurrence of symptoms pointing to liver disease; previous hospitalization or injections; other treatment, if any; onset, duration, frequency, and present status of drug use; dietary and other habits; occupational and family history; alcoholic history, and other possible etiologic agents of hepatitis (drugs and chemicals, industrial poisons, and infections including mononucleosis, tuberculosis or syphilis).

Physical Examination: A complete physical examination was always performed. Special attention was given to signs indicative of chronic liver disease and of opiate addiction.

* Received for publication December 14, 1959.
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Laboratory Data: In most of the patients a complete blood count and routine urinalysis were performed, and some had a serologic test for syphilis, a heterophil agglutination test for infectious mononucleosis, and a photoroentgenogram for tuberculosis. All tests were noncontributory. Nine different "routine" liver function tests were performed at least once in most patients. The tests included:

1. Bromsulfalein retention (BSP), measured in unhemolyzed serum along with a control, by the method of Hiller.[8]

2. Serum glutamic oxalacetic transaminase (SGO-T), using the spectrophotometric method of Karmen.[9]

3. Total and prompt reacting (1′) serum bilirubin, using Malloy and Evelyn's method [10] as modified by Ducci and Watson.

4. Serum protein (TP) with albumin-globulin fractionation (A/G) by the biuret technic, using Kingsley's method.[11]

5. Zinc sulfate turbidity (ZT) test for estimation of total serum gamma globulin, in units (u) derived from a barium sulfate standard as described by Kunkel.[12]

6. Thymol turbidity test (TT), using reagent buffered at pH 7.82, by the method of Maclagen, as modified by de la Huerga and Popper.[13]

7. Serum alkaline phosphatase test in units (u), as described by Gomori.[14]

8. Total cholesterol (TC) and percentage of esters, using the method of Bloor et al.[15]

9. Urinary urobilinogen (semiqualitative) by the tube dilution method, as described by Wallace and Diamond,[16] with a 1:32 dilution as upper limit of normal.

Drug Usage

All 21 members of the group were heroin users, exposed to six common sets of "works" (needle, eye dropper, and rubber bulb), each belonging to a narcotic user who had been previously jaundiced. In addition, seven were occasionally exposed to sources outside the group.

Duration of usage, according to history, ranged from one to five months in three, from six to 14 months in 13, and from 15 to 32 months in five. Patients met an average of once to twice daily, usually in groups of three to four. A total of 12 were currently using the drug, and seven of these admitted having taken heroin within 48 hours prior to a clinic visit.

The route of drug administration was intravenous ("mainline"), and its technic, with needle and eye dropper, similar to that recently reported by Alter and Michael.[1] Methods of sterilization varied greatly among individual users. In most instances the instruments were passed from one person to another without any sterilization.

Case Reports

The following four representative cases are presented in detail. The clinical features in the group as a whole are summarized in the sections that follow.

Case 1. Cholangiolitic hepatitis, symptomatic, with abnormal liver function tests one year later:

This 17 year old boy was hospitalized for jaundice at another hospital from December 18, 1956, to January 25, 1957 (figure 1).

On examination an enlarged liver was felt 9 cm. beneath the costal margin, and moderate ascites was established by paracentesis. Laboratory determinations, including a complete blood count, serologic test for syphilis and heterophil agglutination, were negative. Liver chemical tests showed: SGO-T, 166 units; bilirubin, 6.2, with a 4.7 mg.% direct; alkaline phosphatase, 8.9 units; prothrombin time, 18/12 seconds; cholesterol, 144, with 50% esters. Serum protein with A/G ratio and zinc sulfate turbidity tests were normal.

The patient improved on bed-rest, and at discharge all of his chemical tests were approaching normal: SGO-T, 48 units; bilirubin, 1.5 mg.%; bromsulfalein, 5.0%; alkaline phosphatase, 3.0 units.

Punch biopsies of the liver performed on December 28, 1956, and January 19, 1957, revealed normal gross architecture but on microscopic examination showed distention of the bile capillaries with plugging by bile casts. The liver cells varied in size and staining properties, and contained much bile pigment. Periportal fields and the larger bile ducts were of usual size. The supporting stroma had considerable inflammatory cellular infiltration. The diagnosis of cholangiolitic hepatitis was made.

On the first clinic visit (August 23, 1957), seven months after discharge, the patient complained of vague para-umbilical shooting pains, fatty food intolerance, occasional vomiting, and fatigue. All of these symptoms persisted throughout the four months of observation. Examination was entirely negative except for some antecubital scars and a skin abscess in the left antecubital fossa.

Complete blood count and urinalysis were normal. SGO-T was 222 units; bromsulfalein, 19%; zinc sulfate turbidity, serum protein and A/G ratio, thymol turbidity test, bilirubin, and alkaline phosphatase were normal. In the four succeeding months (up to December 24, 1957), all of the patient's liver chemical tests returned toward normal levels except the SGO-T, which continued to fluctuate within an abnormal range of 222 to 81 units (figure 1).

Comment: Although this patient's disease regressed during hospitalization, eight months later he presented with symptoms and abnormal SGO-T and bromsulfalein tests. These abnormalities persisted during the four months of observation, one year after his original illness.

To test the effect of opiates on SGO-T levels, determinations were made in several patients before and after self-administration of heroin, but no significant changes were observed. These findings contrast with a single recent report from the Mayo Clinic, suggesting that opiates may influence the level of SGO-T.[17] In our series, however, there was no relationship between drug administration and SGO-T values, as illustrated in the next case report.

Case 2. Effect of heroin on SGO-T activity in a patient with chronic hepatitis:

This 17 year old unemployed boy admitted using narcotics with the preceding patient (case 1) in December, 1956. In early February, 1957, he noted anorexia,

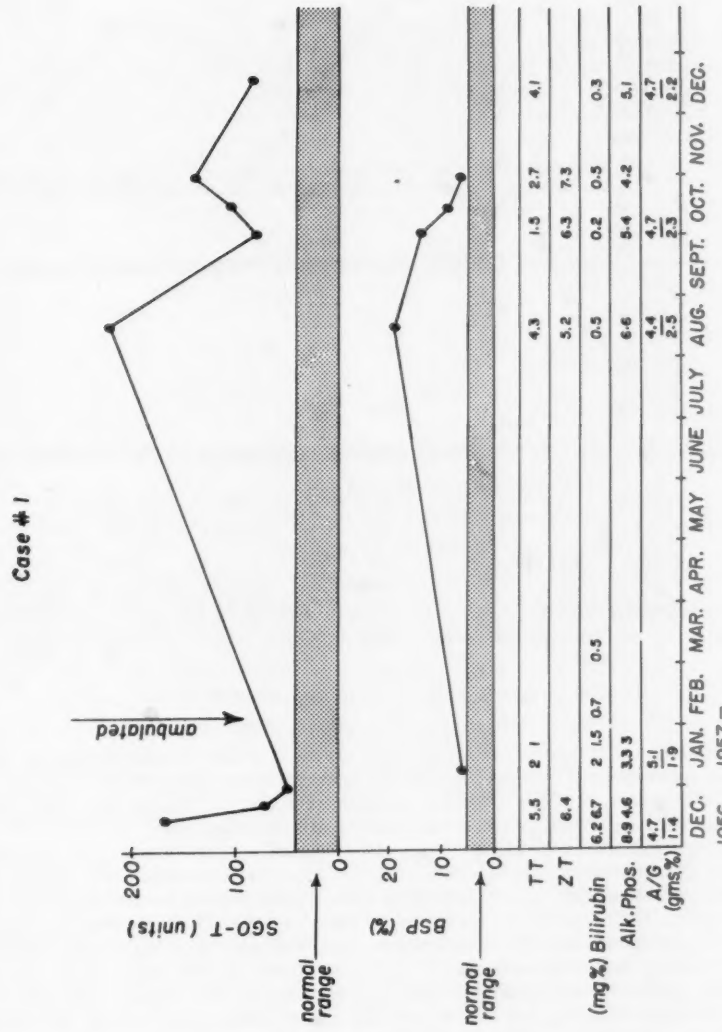


FIG. 1. *Case 1.* Cholangiolitic hepatitis, symptomatic, with abnormal liver function tests one year later.

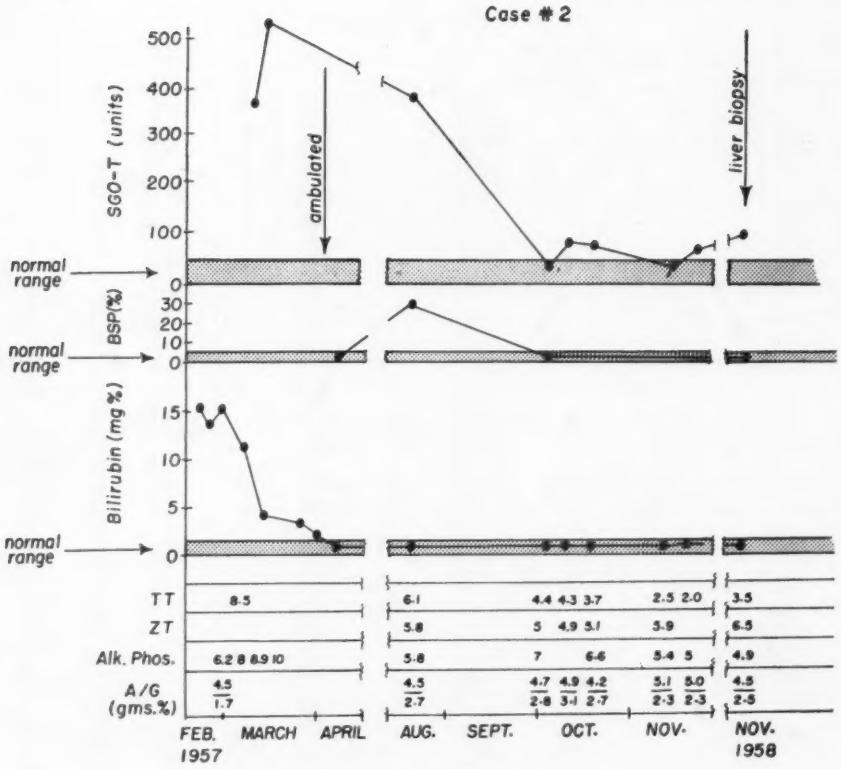


FIG. 2. *Case 2.* Chronic hepatitis with liver biopsy.

malaise, dark urine, nausea, vomiting, light stools, a weight loss of 40 pounds, and fatigue, followed on February 23, 1957 by scleral icterus. He entered a local hospital on February 24, 1957. Positive findings were a palpable liver and generalized icterus. Initial complete blood count, routine urinalysis, serologic test for syphilis, blood urea nitrogen, and glucose all yielded normal results. Liver chemical tests (figure 2) revealed an elevated bilirubin (16.1), thymol turbidity test (8.5), decreased cholesterol esters (144, with 40% esters), and a prothrombin time of 19/13 seconds. SGO-T determinations, first done on March 11, 1957, and then on March 15, 1957, were 366 and 534 units, respectively. The patient was treated with bedrest, a high protein and carbohydrate diet, and vitamins. He continued the use of narcotics, which were "smuggled" into the hospital by his friends, but his liver chemical tests gradually fell toward normal, and at discharge (April 8, 1957), his bilirubin was 0.9 mg.% and his bromsulfalein, 2.5%.

When first seen at the clinic on August 22, 1957, the patient complained of intermittent mild abdominal pains and fatty food intolerance, and a slightly tender liver was felt 6 cm. beneath the right costal margin. In addition, he had many antecubital scars. At the following visits, physical findings and symptoms were no longer present.

Initial laboratory data included a normal complete blood count and urine. Abnormal liver tests were: SGO-T, 383 units; bromsulfalein, 30%; thymol turbidity, 6.1 units; urinary urobilinogen, 1:64. The remaining liver chemical tests were all normal.

A liver biopsy performed on November 10, 1958, 19 months after the initial attack of jaundice, revealed an increased number of round cells in the periportal and parenchymal regions (figures 3, 4, 5). SGO-T on the day of biopsy was 93 units, and the remainder of the liver profile was within normal limits.

This patient was last seen in April, 1959, more than two years after his initial episode of jaundice, and presented with a new physical finding, spider angiomata over his upper extremities and chest. Liver function tests at this time were essentially unchanged. The SGO-T remained the only abnormal test.

The following data relate drug use to SGO-T activity:

Date	Time after Heroin Administration (hours)	SGO-T (units)
8–22–57	14	383
10–3–57	35	38
10–8–57	20	68
10–16–57	12	64
11–12–57	1½	34
	8	31
11–19–57	2½	51
5–27–58	12	40

Comment: This patient had symptoms and signs of active liver disease when first seen by us six months after a well documented attack of hepatitis. Although he improved symptomatically, the persistent fluctuation in SGO-T alerted us to the fact that he had not fully recovered. The liver biopsy 19 months following his hospitalization for hepatitis confirmed the diagnosis of chronic hepatitis. This case illustrates the sensitivity of the SGO-T test as an indicator of subclinical liver disease. Furthermore, the data fail to show any correlation between the SGO-T levels and the time of administration of heroin or adulterants. This observation also held for all other tests of hepatic function.

Case 4. Multiple attacks of jaundice:

This 20 year old electronics technician came to the clinic stating that he had been referred by other members of the group and had had a recurrence of hepatitis. He had begun to use narcotics in February, 1955, while stationed with the Navy in New York, and thereafter continued the use of heroin as often as four times daily.

In April, 1956, the patient had noted a 10-pound weight loss, slight fatigue and yellow sclerae, all of which lasted for one and one-half months and then subsided.

The patient joined this group of heroin users in 1957, and in March of that year again noted yellow sclerae, dark urine, and weakness. He promptly reported to the Naval authorities and was treated symptomatically for hepatitis and drug addiction at the St. Albans U. S. Naval Hospital until the middle of June, 1957, when he was discharged from service. He immediately rejoined the group of heroin users.

When seen at the clinic, in September, 1957, the patient had lost 13 pounds in a 10-day period, and soon thereafter noted anorexia, myalgia, arthralgia, weakness, dark urine and jaundice. Physical examination was unremarkable except for scleral



FIG. 3. *Case 2.* Needle biopsy specimen of liver obtained 19 months after onset of illness. Hematoxylin and eosin stain, original magnification × 14.

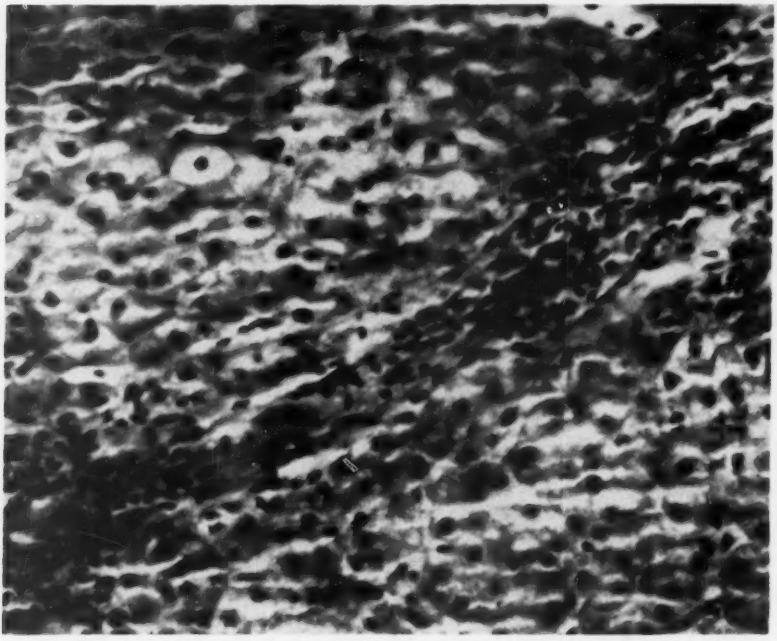


FIG. 4. *Case 2.* Higher magnification of section illustrated in figure 3. × 100.

icterus, a nontender liver felt 6 cm. beneath the costal margin, and needle marks in the antecubital fossae.

Relevant laboratory data included a normal complete blood count and urine, a negative heterophil agglutination test and normal zinc sulfate turbidity test, alkaline phosphatase, and serum protein with A/G ratio. SGO-T was 202 units; bromsulfalein, 33.5%; bilirubin, 1.7 mg.%, with 0.8 mg.% direct; thymol turbidity, 5 units; urinary urobilinogen, elevated to 1:64 dilution.

At the next visit, only three days later, the patient felt perfectly well and his liver was no longer palpable, despite lack of treatment and continuance at his job. His SGO-T had fallen to 45 units, and all of the remaining liver tests had returned to normal. His condition remained unchanged during a three-month follow-up

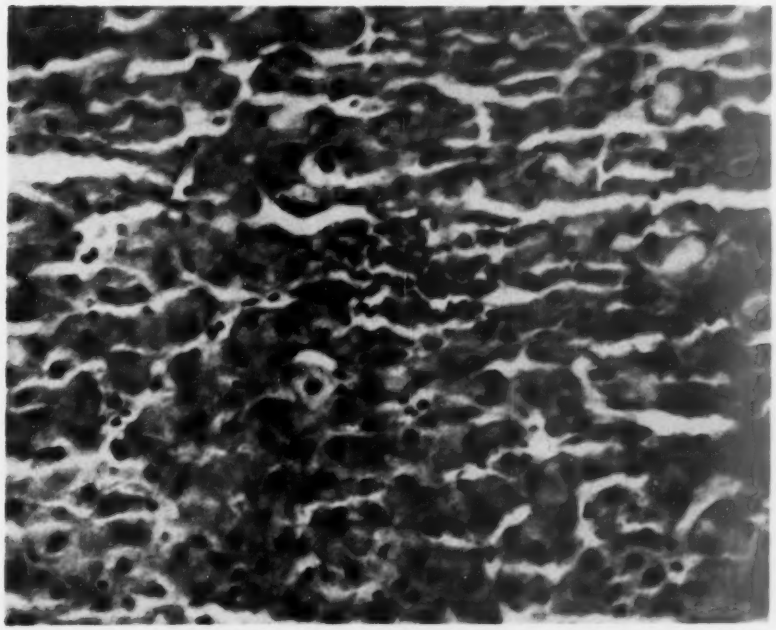


FIG. 5. *Case 2.* Another section of liver biopsy specimen, showing parenchymal round cell infiltrations. × 100.

period except for a single rise of SGO-T to 68 units. When last seen (in December, 1957), he was completely symptom-free and his liver chemical tests, including a bromsulfalein of 4.3%, and an SGO-T level of 25 units, were entirely normal.

Comment: The three attacks of jaundice in this patient were all self-limited, and the course was unrelated to therapy. Havens,[7] who also reported three separate episodes of hepatitis at yearly intervals in a narcotic addict, suggests that they represented infections with different strains of virus that are either immunologically unrelated, or incapable of evoking sufficient antibodies to prevent infection. This explanation may also apply to our patient, since he was exposed to different sources in at least the first

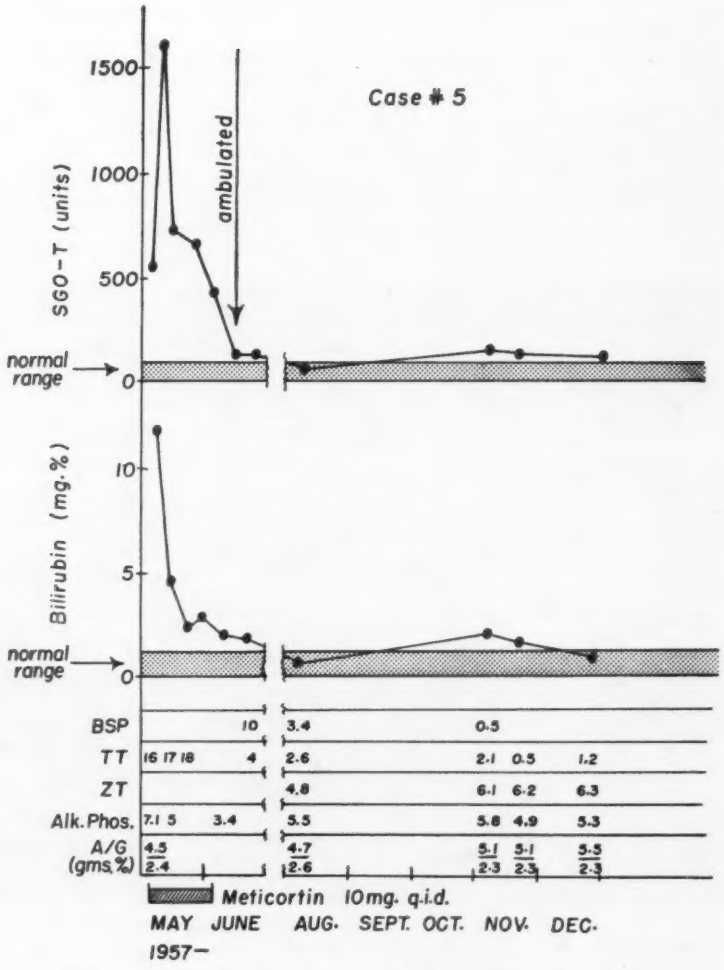


FIG. 6. *Case 5.* Relapse or reinfection of hepatitis in a patient treated previously with Meticorten therapy.

and possibly in the second instance of recurrent jaundice, and since the intervals between attacks were so long.

Case 5. Relapse or reinfection of hepatitis in a patient treated previously with Meticorten therapy:

This 17 year old boy began to use heroin in December, 1956, and continued its use daily thereafter until admitted to The New York Hospital on May 17, 1957, for jaundice (figure 6). One day prior to admission his SGO-T was 554 units.

On admission the patient was febrile (38.2° C.), and had a palpable, tender liver

and spleen, both felt 7 cm. beneath the costal margins. There were no other abnormal physical findings. Extensive laboratory data were noncontributory except for a relative lymphocytosis of 79%, a positive heterophil agglutination test to 1:448 dilution (corrected for Forssmann antibody), the presence of bile and urobilinogen to 1:64 dilution in the urine, and an SGO-T of 1,712 units, associated with markedly elevated liver function tests, as shown in the graph (figure 6). Because of the liver chemical tests and a clinical picture compatible with severe hepatitis, the patient was placed on Meticorten, 10 mg. four times a day for 18 days.

The patient was discharged on June 19, 1957, with normal liver function tests except for an SGO-T of 70 units and a bromsulfalein of 10% retention. On July 11, 1957, he was examined and found to be in excellent health.

On August 22, 1957, when he was first examined in the liver clinic, the patient had no complaints, but admitted to periodic "fixes" with heroin. Physical examination was entirely negative; liver chemical tests, including an SGO-T of 35 units and total bilirubin of 0.50 mg.%, were normal. However, a faint trace of bile and a 1:64 dilution for urobilinogen were present in the urine.

On the patient's next visit, four and one-half months after discharge (November 5, 1957), his SGO-T had risen to 62 units and his bilirubin to 1.62 mg.%, with 1.48 mg.% in the indirect fraction. The following week his SGO-T was 45 units, and bilirubin was 1.38 mg.%, with 1.18 mg.% in the indirect fraction.

When the patient was last seen (December 24, 1957), his SGO-T remained unchanged at 45 units, but his bilirubin had fallen to 0.82 mg.%. There were no specific symptoms referable to liver disease, and physical examination remained normal throughout.

Comment: This case illustrates an asymptomatic relapse or reinfection, revealed only through laboratory studies, occurring six months after the initial attack, in a patient who received optimal treatment, including Meticorten therapy.

Results

Clinical Features: At the time of their initial visit, 12 patients were working, six were unemployed and three were attending school. Thirteen of the 21 patients (table 1A) had a history of jaundice occurring at least four months before the initial clinic visit. Five of the 13 patients had had multiple attacks of jaundice. The most common symptoms were weight loss, a distaste for cigarettes, dark urine, abdominal pain, nausea, vomiting and malaise. Eight of these patients were hospitalized, and three signed out against advice. One patient was treated by us at home, and the remaining four were without medical advice.

Six of the 13 patients recovered completely in a six- to eight-month period, but five still had symptoms of fatty food intolerance, fatigue and abdominal pain. Six patients had abnormal tests when last seen, 4, 5, 6, 11, 18 and 19 months after their initial illness.

Among the eight patients without previous history of jaundice (table 1B) when first seen at the clinic, only one gave a history compatible with hepatitis (case 20); the rest were asymptomatic. None was hospitalized or under medical care.

TABLE IA

Laboratory Data Relative to Liver Functions. Maximal Recorded Values for Each Patient. Patients with History of Jaundice More Than Four Months Earlier

Case	SGO-T Units	BSP Retention %	Alk. Phosph. Bodansky Units	TT Units	ZT Units	Serum Bilirubin mg.%		Serum Cholesterol mg.%		Serum Proteins		Urine Urobilinogen
						Direct	Total	Total	Free	Albumin gm.%	Globulin gm.%	
Normal	5–40	<5	<8	<4	5–12	<0.3	<1.0	150–250	40–70	>4.5	<2.5	<1:64
1*	222	19.0	6.60	4.30	7.29	.10	0.46			4.68	2.33	1:32
2*	383	30.0	7.00	6.10	5.91	.08	0.40			5.31	2.43	1:64
3	34	3.30		1.56	8.36	.20	0.70	131	74.8	5.07	2.53	1:16
4*	202	33.5	6.95	5.00	7.42	.80	1.70			5.52	3.05	1:64
5*	62	3.30	5.82	2.60	6.30	.14	1.62			5.46	2.24	1:64
6*	63	1.30	8.10	2.00	4.69	.10	0.70			4.90	2.08	1:8
7	25	0.98	4.10	2.00		.00	0.60	178	48.2			1:32
8	70									3.38	3.54	1:32
9	51		6.21	2.90	8.60	.08	0.68			5.43	2.39	
10*	54	1.96	8.96	5.10	7.59	.12	1.20			4.98	2.65	1:64
11	31	10.21	3.40	4.16	12.6	.02	0.40	122	72.1	4.23	2.77	
12*	40	4.67	2.10	5.00	9.19		2.30			4.81	2.60	1:64
13*	31		11.0			.06	0.88			4.97	2.41	

* Hospitalized for hepatitis (more than four months prior to initial clinic visit).

Among the entire study group, diets had been poor in six patients since the onset of drug usage, but in none were they currently inadequate. Three patients admitted to more than three beers or one ounce of whiskey a day. In 12 others, alcoholic consumption was limited to minimal weekend drinking.

Physical Examination: There were no signs of liver disease in the group of patients without history of jaundice. In the group with a history of recent jaundice, positive findings were minimal, and were limited to four patients. They consisted of an enlarged liver in three, tenderness to shock fist percussion in two, spider angiomata in two, and scleral icterus alone in one. No other stigmata of liver disease were present.

TABLE IB

Laboratory Data Relative to Liver Functions. Maximal Recorded Values for Each Patient. Patients Without History of Jaundice

Case	SGO-T Units	BSP Retention %	Alk. Phosph. Bodansky Units	TT Units	ZT Units	Serum Bilirubin mg.%		Serum Cholesterol mg.%		Serum Proteins		Urine Urobilinogen
						Direct	Total	Total	Free	Albumin gm.%	Globulin gm.%	
Normal	5–40	<5	<8	<4	5–12	<0.3	<1.0	150–250	40–70	>4.5	<2.5	<1:64
14	49		6.30	1.47	5.07	.08	0.98			5.17	2.60	
15	41		4.32	4.55	7.29	.06	0.46			5.02	3.11	
16	45	4.13	3.66	2.30	5.37		0.34			4.53	1.84	1:32
17	48	2.50	6.57	1.90	6.16		0.28			4.85	2.70	
18	56									4.61	2.65	1:32
19	178	5.65	7.20	3.00	4.40	.14	0.52			5.37	2.23	1:16
20	712	19.0	7.21	3.32	9.97	.10	0.90	152	74.4	4.93	2.37	1:16
21	25		10.1	2.15	3.37	.08	0.30			4.58	1.84	

Local signs of narcotic use observed in seven patients consisted of bluish discoloration or scars over the antecubital fossae. Three of these developed superficial abscesses in the same areas.

All patients were in good general health, and other physical signs, when present, were noncontributory.

Laboratory Tests (Table 1): As noted in table 1, most of the liver function tests were within normal limits. The tests most frequently abnormal were the bromsulfalein and SGO-T, and the latter correlated best of all with the clinical course. It was elevated in three subjects even in the pre-icteric stage.

Discussion

This group of ambulatory patients had a surprisingly high incidence of subclinical liver disease which might have been overlooked in the absence of follow-up studies.

Murray [18] found that approximately 50% of persons receiving icterogenic material contracted hepatitis. Of these, 12% were anicteric and were recognized only by complete clinical and laboratory data. The value of such a careful follow-up study is confirmed here, especially in the eight nonjaundiced patients, who were asymptomatic but were investigated because of their drug addiction, which involved the use of needles in common with the rest of the study group. The levels of SGO-T among these eight were slightly above normal for young adults. Only one (case 21) had a level below 40 units. This patient became sick (without jaundice) two months later, and the SGO-T rose to 380 units. In another eight months the symptoms disappeared and the SGO-T was again 25 units. Case 14, when first seen, had two base line readings of SGO-T, 44 and 49 units, respectively, and was asymptomatic. Six months later this patient developed frank jaundice. Similarly, case 17 was asymptomatic, with SGO-T levels of 44 and 48 units when first seen, and developed jaundice one year later, with an SGO-T of 684 units, which fell to 41 units 11 days later. Four months thereafter he had an episode of anicteric hepatitis, with an SGO-T of 666 units, which dropped to 76 units six days later, after he had been under observation for 16 months. Case 19 started using common needles with cases 1 and 2 of the jaundiced group, and eight and nine weeks later, although asymptomatic, gave respective SGO-T values of 106 and 178 units.

The one anicteric patient who had symptoms of hepatitis when first seen (case 20) never developed jaundice but had an SGO-T of 189 and 414 units. Following an uneventful clinical recovery, he demonstrated persistently high SGO-T levels. After six months of observation, but with no symptoms, his SGO-T reached a peak of 712 units and the bromsulfalein retention was 19%. When last seen, nine and one-half months following his initial illness, he was still in good health; his bromsulfalein was normal, but the SGO-T was elevated (141 units).

Hepatic dysfunction in the absence of any known exposure to hepatotoxic agents has been reported to reach an incidence of 5% in certain groups of young adults.[19] In the present study, 50% of patients gave abnormal results in one or more liver function tests. The SGO-T activity proved to be the most sensitive reflector of both subclinical and chronic hepatic involvement in homologous serum hepatitis, a finding analogous to that recently reported for infectious hepatitis.[20, 21]

The explanation for the unusually high incidence of persistent hepatic dysfunction in this group of young adults is not readily apparent. Poor diet, alcoholism, continued use of narcotics, inadequate treatment and strenuous activity do not seem to be significant factors. In the absence of any other obvious explanation, reinfection with the same or with different strains of virus remains a real possibility.

Summary

A group of 21 youthful narcotic users exposed to six common needles was studied over an 18-month period. The drug used was heroin, the duration of usage averaged 10 months, and the mode of administration was by the intravenous route.

Of the 21 patients, 13 gave histories of one or more attacks of jaundice. All of these patients were at least four months convalescent at the onset of the follow-up study.

Only four of these patients showed definite clinical signs and symptoms indicative of liver disease. On the other hand, chemical evidence of liver dysfunction was present in 14 of the entire group of 21 patients, as indicated by elevations in the SGO-T, with levels as high as 712 units. The bromsulfalein test correlated closely with the SGO-T levels, but other liver function tests were of less significance as indicators for detecting hepatic dysfunction. The SGO-T test was not influenced by administration of narcotics.

Case reports are presented which illustrate the high incidence in this group of patients of persistent or recurrent liver disease following hepatitis. In addition, the usefulness of the SGO-T test in the detection of subclinical liver disease is demonstrated.

Acknowledgment

The authors wish to acknowledge the technical assistance of Nathan Brot, Carlos Santiago and Eleanor Darcy in the laboratory determinations.

Summario in Interlingua

Le presente reporto describe un guppo de 21 usatores juvenil de narcotico, exponite a un provision commun de agulias, qui esseva observate a base ambulatori durante un periodo de 18 menses. Le droga usate esseva heroina; le modo de administration per via intravenose.

Inter le 21 patientes, 13 reportava antecedentes de un o plure attaccos de jalnessa. Omne le 13 se trovava in stato de reconvalescentia depost al minus quatro menses al tempore del initiation del presente studio. Sex de illes se restabliva completemente intra periodes de inter sex e octo menses. Sex alteres manifestava anormalitates in tests de function hepatic al tempore de lor ultime visita, i.e. quatro, cinque, sex, 11, 18, e 19 menses, respectivemente, post lor morbo initial.

Ex le octo patientes primo vidite sin previe experientia de jalnessa, tres disveloppava subsequentemente jalnessa franc, e quatro habeva episodios de hepatitis anicteric.

Definite signos e symptomas clinic de persistente morbo hepatic esseva presente in solmente quatro del patientes. Del altere latere, provas chimic de dysfunction hepatic esseva trovate in 14 del gruppo total de 21. Iste alte incidentia de morbo hepatic subclinic esseva demonstrate per le constatation de valores elevate pro le retention de bromsulfaleina e le nivello seral de transaminase glutamic-oxaloacetic. Le resultatos del secunde de iste duo tests monstrava le melior correlation con le curso clinic. Altere tests de function hepatic esseva minus significative como indicatores de dysfunction hepatic. Le test pro transaminase glutamic-oxaloacetic esseva le sol con resultatos anormal in tres patientes in le stadio pre-icteric de lor morbo e in le quatro con episodios de hepatitis anicteric. Le test non esseva influentiate per le administration de narcoticos o de adulterantes. Es presentate reportos de casos individual como illustration del utilitate del test pro transaminase glutamic-oxaloacetic del sero in le detection de subclinic morbo hepatic.

Le explication del inusualmente alte incidentia de persistente o recurrente dysfunction hepatic in iste gruppo de juvene adultos non es immediatemente apparente. Factores como inadequatia del dieta, uso continue de narcoticos, insufficientia del tractamento, e excessos de activitate non pare esser significative. In le absentia de altere obvie explicationes, re-infection con le mesme o con un altere racia de virus remane clarmente un possibilitate.

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PERCUTANEOUS NEEDLE LIVER BIOPSY IN MALIGNANT NEOPLASM WITH SPECIAL REFERENCE TO MYELOID METAPLASIA *

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The general clinical value of percutaneous needle biopsy of the liver is widely recognized. Its use in an institution devoted to the diagnosis and study of neoplasia has certain special characteristics which frequently enable the investigator to direct therapy or research in a more efficient manner. At the same time it might be expected that, because of the often involved clinical situations presented, as well as the debilitation of cancer patients in general, complications might occur more frequently than usual following biopsy.

The purpose of the present paper is to assess more clearly these particular values of liver biopsy in neoplastic disease, as well as to evaluate morbidity and mortality directly related to the procedure. The report covers experience with 330 biopsies in 280 patients during the period of January, 1955, to June, 1959.

Material and Methods

All patients were referred for study and treatment because of suspected or proved neoplastic disease. The age groups are those commonly seen in malignant disease, and are shown in table 1. As expected, almost all fall within the 30- to 80-year period, the three largest groups being in the fifth, sixth and seventh decades of life. All types of neoplasia are represented. The method of biopsy has been previously described, and, briefly, consists of the use of a specially modified Silverman needle and a standard technic.[5] Biopsies performed in this manner are completed within two seconds, and the depth of the liver may be located rather precisely. When tumor involvement is strongly suspected, multiple biopsies are taken. If the liver is enlarged below the costal margin, transabdominal as well as transthoracic biopsy sites are used. When the liver is not enlarged, two specimens are taken at the same transthoracic site, with the needle angled to obtain material from different liver areas. As noted by others,[7] tumor invasion may be discovered in the transthoracic specimen, even when the liver appears to be enlarged and nodular in the area of the transabdominal biopsy, which is

* Received for publication December 29, 1959.

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TABLE 1

Age Distribution

Age Group	No. of Patients
10–20	2
21–30	7
31–40	22
41–50	57
51–60	75
61–70	84
71–80	31
81–90	2
Total	280
Male	166
Female	114
Total	280

reported as negative. No complication in our experience has been related to multiple biopsies taken during a single procedure. Biopsy is always performed on the ward, and the usual precautions as to bleeding tendencies and aftercare are observed.[5, 12] Enough material is regularly obtained to permit bio-assay or histochemical studies, as well as histologic examination.

The patient material covered in this study naturally divided itself into the following categories: (1) confirmed neoplasia, further subdivided into those with (a) specimens showing tumor involvement, and (b) biopsy specimens without evidence of tumor; (2) patients referred for suspected neoplastic disease, not confirmed, in whom liver biopsy was performed with the object of proving metastatic or primary liver involvement, or because of evidence of liver disease; (3) leukemias, lymphomas, and miscellaneous anemias or blood dyscrasias admitted on the hematology service. The numbers of patients and biopsies in each category are shown in table 2. In three patients, either an inadequate specimen or none was obtained.

CONFIRMED NEOPLASTIC DISEASE

In known neoplasia, the course of treatment may be radically affected by the findings of liver involvement. While metastatic liver disease may be suspected on the basis of abnormal function tests and physical findings, histo-

TABLE 2

Total Series of Biopsies
January, 1955, to June, 1959

	Patients	Biopsies
Confirmed malignant neoplasm		
1. With positive liver biopsies	65	77
2. With negative liver biopsies	96	110
Malignant neoplasm not confirmed	58	74
Leukemias, lymphomas and miscellaneous	58	66
Inadequate specimens	3	3
Total	280	330

logic proof is often necessary to prevent unnecessary surgery, or to direct treatment along radiologic or chemotherapeutic lines. In primary hepatoma, liver biopsy and isotope scanning technics may indicate enough uninvolved liver to make an attempt at resection feasible. The probabilities of a positive biopsy in metastatic disease have been thoroughly discussed elsewhere;[2, 3, 4, 6, 7, 10, 11] they are surprisingly good. Tumor has been detected in as many as 76% of suspected cases.[2]

The group of patients reported (table 2) were referred as known malignant neoplasia, or were determined to have metastatic or primary neoplasm following biopsy. In the attempt to determine the accuracy of the method, the largest source of error was found to be inadequate follow-up (table 4). If these cases are included with the specimens proved false-negative by autopsy or surgery, liver biopsy was successful in demonstrating tumor in 75.1% of all proved malignant neoplasms. It is probable that

TABLE 3

Malignant Neoplasia with Positive Liver Biopsies

Type	Patients	Biopsies
I. Primary carcinoma of the liver		
A. Hepatocellular	3	6
II. Metastatic		
A. Adenocarcinoma	33	37
B. Unclassified	20	23
C. Melanoma	2	2
D. Carcinoid	3	5
E. Anaplastic	1	1
F. Small cell	2	2
G. Neuroblastoma	1	1
Total	65	77

some of this group of 28 patients did not have neoplastic invasion of the liver at the time of biopsy, but, since they could not be checked, they are scored against the method. The most common complicating benign diseases were shown to be infectious hepatitis (13 cases) and cirrhosis (12 cases). Normal liver was obtained in 23 patients, in whom the results were proved to be correct by autopsy, surgery or adequate follow-up. Criteria for follow-up were six months' observation without physical or laboratory evidence of hepatic disease.

Types of tumor involvement are listed in table 3. Primary neoplasm was proved in three instances, although in three other cases, listed as "unclassified," it was suspected but could not be confirmed because of inadequate follow-up. The large group of unclassified biopsies (23 specimens in 20 patients) illustrates the difficulty of identifying the type of parent tumor in many instances.

NON-NEOPLASTIC DISEASE

This group of patients, referred as diagnostic problems, possibly neoplastic, were biopsied in an attempt to reach an early diagnosis. All had

physical or laboratory evidence of liver disease, although in some instances such evidence consisted largely of hepatomegaly, and in others of slight alterations of liver function studies. As in the neoplastic group, the most commonly confirmed diseases were cirrhosis (12 cases) and hepatitis (six cases). In the other 40 cases, biopsy was performed in a variety of benign diseases, with nondiagnostic changes noted on the biopsy specimen (table 4). In few of these cases could the biopsy be called helpful, except in a negative sense, undoubtedly reflecting patient selection in a cancer institute.

TABLE 4

Negative Liver Biopsies
Malignant Neoplasm

	Patients	Biopsies
I. Associated benign diagnosis		
A. Infectious hepatitis	13	16
B. Cirrhosis	12	12
II. Proved negative biopsies		
A. By operation	9	11
B. By autopsy	9	15
C. By adequate follow-up	15	16
III. False-negative		
A. By autopsy and surgery	10	10
IV. Inadequate follow-up	28	30
Total	96	110
Non-neoplastic Disease		
I. Cirrhosis	12	14
II. Hepatitis	6	16
III. Normal liver or nondiagnostic changes	40	44
Total	58	74

LEUKEMIA, LYMPHOMA AND MISCELLANEOUS HEMATOLOGIC PROBLEMS

Biopsy was carried out in a variety of hematologic disorders at the request of the hematology section (table 5). In the leukemias, the objective in most cases was the clarification of physical and laboratory evidence of liver damage during the course of the disease. In two instances, myeloid metaplasia was suspected and proved by biopsy. A total of six (one of myeloid and five of lymphocytic leukemia) showed the cellular infiltrate characteristic of the disease. In the majority of patients, some type of chemotherapy had been employed. No histologic evidence of liver cell damage was found in any such case.

In the group of lymphomatous diseases, biopsy was employed to detect neoplastic invasion of the liver, and to attempt to determine the cause of evidence of liver damage. Characteristic infiltration was discovered in five of 14 cases of lymphoma, but in none of 14 cases of Hodgkin's disease and two cases of reticulum cell sarcoma. In Hodgkin's disease, autopsy showed

four of these negative results to be correct and six to be incorrect. Again, many of these patients had received chemotherapy without histologic evidence of liver cell damage.

In the miscellaneous group, three cases of sarcoidosis showed granulomatous change in two, and myeloid metaplasia was noted in two instances of undiagnosed anemia. None of the other patients (three with multiple

TABLE 5

Leukemia, Lymphoma and Miscellaneous Hematologic Problems

	Patients	Biopsies	Positive	Proved
I. Leukemia				
A. Myeloid	4	4	3* (2 with myeloid metaplasia)	1 (correct)
B. Lymphocytic	7	9	5*	3 (correct)
C. Monocytic	1	1	0	
II. Lymphomas				
A. Lymphomas	14	15	5†	3 (correct)
B. Hodgkin's	14	14	0	10 (4 correct) (6 incorrect)
C. Reticulum cell sarcoma	2	2	0	
III. Miscellaneous				
A. Sarcoidosis	3	3	2‡	
B. Polycythemia vera	1	1	0	
C. Multiple myeloma	3	4	0	
D. Myeloid metaplasia	2	2	2	
E. Pernicious anemia	3	7	0	
F. Anemia, etiology unknown	3	3	0	
G. Sickle cell	1	1	0	
Total	58	66	17	

* Leukemic infiltrate.
† Lymphomatous infiltrate.
‡ Granulomatous infiltrate.

myeloma, one with polycythemia vera, three with pernicious anemia, one with sickle cell anemia, and three with anemias of unknown etiology) exhibited changes of diagnostic significance in the liver biopsy specimen.

Our experience tends to show that, while leukemic and lymphomatous infiltrate may be found in an appreciable number of cases, Hodgkin's disease is difficult to demonstrate by needle liver biopsy. Except in myeloid metaplasia, liver biopsy was of no positive help in determining the source of anemia of obscure etiology.

COMPLICATIONS

The only complication noted in this series, except for transient slight to moderate pain at the biopsy site, was intra-abdominal hemorrhage. Bleeding occurred in six instances, with three deaths. These six cases are reported in detail in an attempt to clarify the cause of hemorrhage.

Case Reports

Case 1. A 52 year old white female was first seen June 30, 1958, with carcinoma of the breast and extensive bone metastases which had been treated by x-ray therapy to the pelvis and spine in October, 1957. This was followed by combined testosterone and radioactive phosphorus (P^{32}) therapy in January, 1958. Following the P^{32} therapy there was an episode of severe pancytopenia, treated by transfusions. The patient's blood count had been relatively normal until June, 1958, when the hemoglobin fell to 8.1 gm. Abnormal liver function tests had been noted since March, 1958, consisting of bromsulfalein retention, 46.7%; thymol, 12.2 units; and cephalin flocculation, 4 plus. The liver was palpable 3 cm. below the right costal margin; a biopsy performed July 2, 1958, showed focal fibrosis, but no tumor. At the time of biopsy, platelets were 64,000; hematocrit, 32; white cells, 2,600; red cells, 3,250,000; hemoglobin, 10.8 gm.; prothrombin activity, 100%; reticulocyte count, 1.9%. The platelet count three weeks previously had been 140,000; hematocrit, 32; white blood cells, 5,600. One hour after the biopsy the patient went into shock, but recovered within three hours on 1,000 c.c. of whole blood intravenously, together with intravenous and intramuscular cortisone. She was continued on treatment, and was seen one year later with multiple metastases to bone and skin, and probably to the viscera, as evidenced by abdominal masses. There were bilateral pleural effusion, ascites and anemia, leukopenia and thrombocytopenia, with a platelet count of 38,000.

Case 2. A 39 year old white female had had a radical mastectomy in February, 1958, with postoperative irradiation for carcinoma of the breast. Six months later she experienced easy fatigability, back pain and anorexia, and her liver was found to be enlarged 7 cm. below the right costal margin. On admission to the hospital for the purpose of diagnostic liver biopsy, white cells were 12,600, and hemoglobin was 15.1 gm., and there was a moderate polychromatophilia, with 42 nucleated red cells per 100 cells. Alkaline phosphatase, 15.1 units; bromsulfalein retention, 31.5%; total serum protein, 8.1; albumin, 5.8; globulin, 2.3 gm.%; bilirubin, 0.84 mg.%; thymol turbidity, 1.5 units. Prothrombin activity was 100%, but the platelet count was not reported at the time of biopsy. One hour after biopsy the patient went into shock, which was rapidly controlled by administering 1,000 c.c. of blood intravenously. Evidence of peritoneal irritation developed several hours later, but subsided without incident. The platelet count was found to be 20,000. The liver biopsy showed miliary metastatic carcinoma of the liver with severe extramedullary hematopoiesis. The patient died one month later, and an autopsy showed metastatic breast carcinoma in liver, spleen, lymph nodes and bone, with desmoplastic fibrosis of marrow spaces and total displacement of marrow, as well as extramedullary hematopoiesis in liver and spleen. A skeletal x-ray survey had shown no evidence of bone metastases at the time of biopsy.

Case 3. A 75 year old white female with an established diagnosis of chronic myelogenous leukemia, who had been treated with Myleran for long periods, was admitted with shortness of breath and markedly enlarged liver and spleen. A group of liver tests on January 28, 1957, showed total serum protein, 7.5 gm.%; alkaline phosphatase, 4.7 units; thymol turbidity, 12.2 units; serum bilirubin, 0.10 mg.%; bromsulfalein retention, 7.4%; cephalin flocculation, 4 plus. Prothrombin activity, 82%; platelets, 500,000; white blood cells, 86,000; hemoglobin, 13.6 gm. A liver biopsy showed rather marked myeloid metaplasia. Following the biopsy the patient complained of severe right upper quadrant pain for days; there was marked tenderness in this area, and a subcapsular hematoma was clinically diagnosed. No transfusions were required. Two years later there was little change in her condition, and she had required intermittent blood transfusions during this interval for anemia.

Case 4. This 70 year old white female was admitted in March, 1958, with a

diagnosis of carcinoma of the bladder. Because of anemia she was transfused and then placed on supervoltage x-ray therapy. By April 11, 1958, she had received a tumor dose in excess of 1,540 roentgens, and was still on treatment May 6, when it was noted that she was definitely icteric, with a slight elevation of temperature, and an enlarged and tender liver. Alkaline phosphatase was 75.6 units; serum bilirubin, 10.56 mg.%; thymol turbidity, 2.22 units; cephalin flocculation, 4 plus; serum proteins, 6.5 gm.%, with a normal albumin/globulin ratio. Prothrombin activity, 84%; platelets, 66,000; white blood cells, 2,400; hemoglobin, 10.0 gm. Infectious hepatitis was suspected, and a liver biopsy carried out May 14, 1958, confirmed this diagnosis. The patient was watched routinely for 24 hours, during which there was no change in the pulse or blood pressure. Her abdomen was examined approximately eight hours after biopsy, and no abnormalities were noted except for a certain amount of pain at the biopsy site. Meticorten therapy was begun the day following biopsy, but on the following morning, 40 hours after the biopsy, it was noted that her color was poor and her pulse rapid, and she soon died. Autopsy revealed a small subcapsular hematoma, hemoperitoneum, and a small puncture wound without tear over the right lobe of the liver. An invasive transitional cell carcinoma of the bladder, acute viral hepatitis and chronic pyelonephritis of the right kidney, with right hydronephrosis and hydro-ureter were found present. In addition, a marked calcific aortic stenosis, quiescent rheumatic myocarditis, and atherosclerosis of the coronary arteries were noted. The pathologist listed the immediate cause of death as hemorrhage following liver biopsy, which would appear to have been delayed.

Case 5. This 62 year old white female with chronic lymphatic leukemia had been treated intermittently over a period of three years with Purinethol. On July 13, 1956, she was noted to be jaundiced following a course of treatment. Serum bilirubin, 12.8 mg.%; thymol turbidity, 19.2 units; serum proteins, 6.4 gm.%; albumin, 4.2, and globulin, 2.2, with alkaline phosphatase, 19.0 units, and cephalin flocculation, 3 plus. Prothrombin activity was 68%; and platelets, 96,000. The patient was thought to have infectious hepatitis, but a liver biopsy July 19, 1956, showed only leukemic infiltrate in the liver. Jaundice subsided gradually, and she improved clinically when Purinethol therapy was discontinued. Another liver biopsy (August 14, 1956) showed essentially the same findings, the prothrombin activity and platelet count on this occasion being approximately the same as on the first biopsy. During 1957 she received intermittent Purinethol therapy, but was re-admitted May 29, 1958, because of recurrence of jaundice on Leukeran therapy, begun May 9, 1958. The serum bilirubin rose rapidly to 26.40 mg.%; thymol turbidity, 9.62 units; serum proteins, 6.2 gm.%, with a normal albumin/globulin ratio; alkaline phosphatase, 6.2 units; cephalin flocculation, 2 plus. Prothrombin activity, 74%; platelets, 92,000. Liver biopsy was again performed, and after 30 minutes the patient went into shock, with absent blood pressure. She was massively transfused and taken to surgery, and a small puncture hole in the liver was closed with omentum. Despite all therapy she died, and permission for autopsy was not obtained.

Case 6. This 65 year old white male was admitted June 4, 1957, with weakness and abdominal distention. There was a marked generalized lymphadenopathy, and the spleen was grossly enlarged. Hemoglobin, 10.3 gm.; white cells, 31,500; platelets, 72,000. A tentative diagnosis of chronic myelogenous leukemia and/or myelofibrosis with myeloid metaplasia of the liver and spleen was made. Liver function studies were not remarkable except for a thymol turbidity of 12.6 units, and cephalin flocculation of 4 plus. Prothrombin activity was 59%; platelets, 74,000; and white blood cells 55,000, at the time of biopsy. Fifteen minutes after the procedure the patient went into shock, with absent pulse and blood pressure. He was massively and rapidly transfused, and a laparotomy disclosed a small needle puncture in the right lobe of the liver, which bled profusely. The area was packed, and the blood pressure

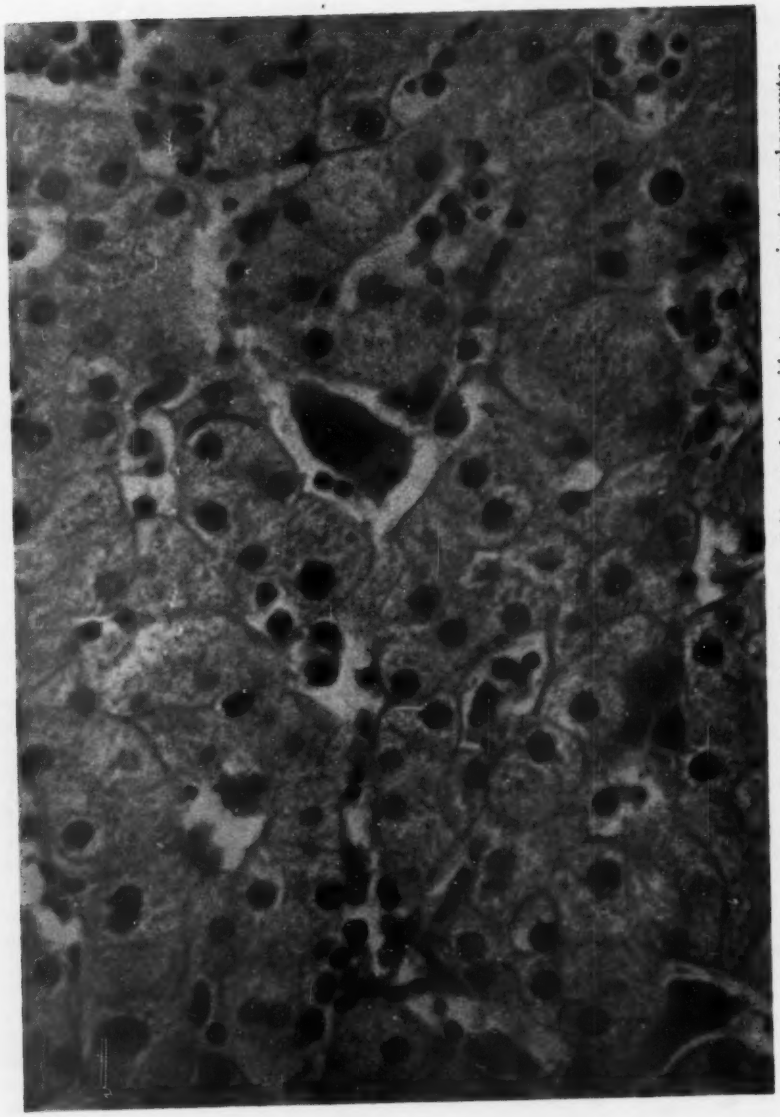


FIG. 1. *A*. Liver biopsy section in case 6, showing myeloid metaplasia, with two prominent megakaryocytes.

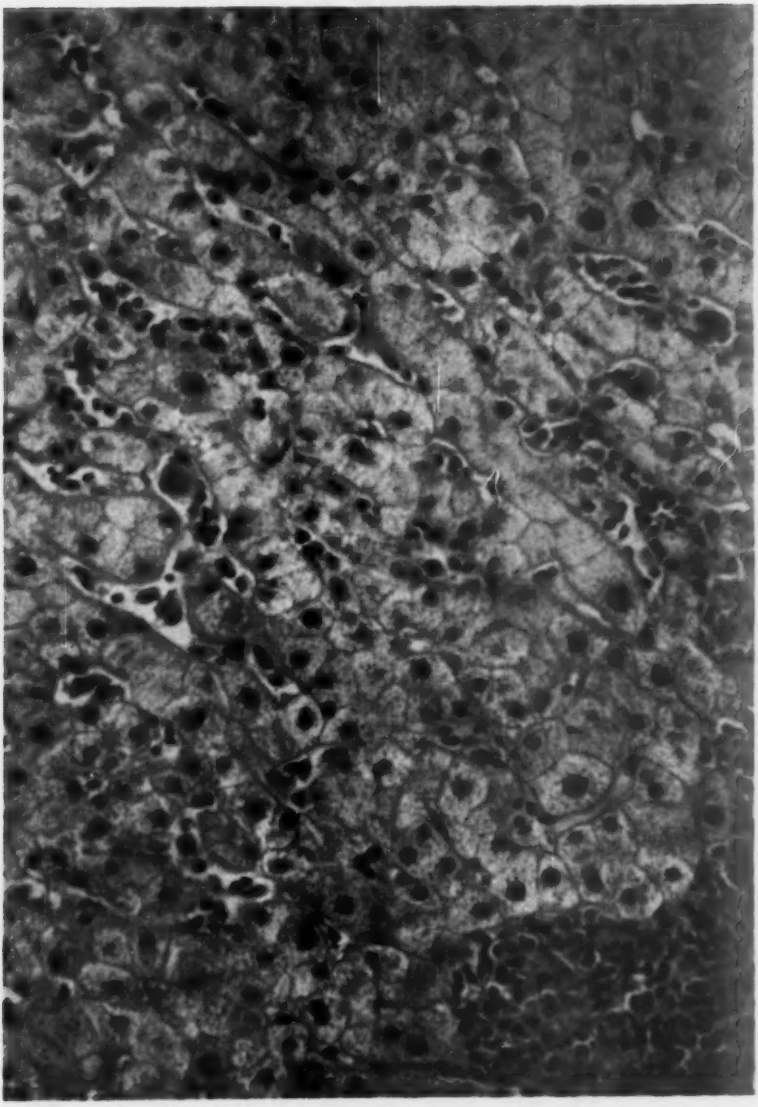


FIG. 1. *B.* Extensive leukemic infiltrate in case 6, noted in liver biopsy.

rose to 120/80 mm. of Hg, but two hours later he again went into shock and died. The liver biopsy revealed extensive myeloid metaplasia, with many granulocytes. Postmortem examination showed chronic granulocytic leukemia, and leukemic infiltration of liver, spleen, kidneys, abdomen, pancreas, lymph nodes, lungs, heart and small intestines, with myeloid metaplasia of spleen and liver, as well as hemoperitoneum.

Myeloid Metaplasia

In a review of the complications in this series, it was noted that three instances of bleeding occurred in patients showing myeloid metaplasia of the liver. In two instances (cases 3 and 6) this finding was associated with leukemia, while in the third (case 2) there was a marked infiltration of the bone marrow with breast carcinoma. In two other cases that demonstrated myelofibrosis of the bone marrow and myeloid metaplasia of the liver on biopsy (table 5), no bleeding occurred. Thus, in a total of five cases with this finding, three exhibited hemorrhage. Further analysis revealed that the most severe bleeding occurred in the two patients with lowered platelet counts (20,000 and 74,000, respectively). In the case developing the subcapsular hematoma (case 3), the platelet count was 500,000, while in the two with myelofibrosis without hemorrhage the counts were 118,000 and 128,000, respectively. Prothrombin activities in all instances were well within ranges considered to be safe by experienced observers,[8, 12] ranging from 59 to 100%.

Since myeloid metaplasia of the liver has been associated with half of the cases of hemorrhage in this series, we have become cautious about employing diagnostic liver biopsy in any patient when this finding is suspected. The cause of increased incidence of hemorrhage with myeloid metaplasia of the liver is not evident, and may be more clearly related to the accompanying bone marrow defect than to hemorrhagic tendencies within the liver itself. The relatively normal platelet counts in the two patients who did not hemorrhage would tend to support this view.

Other Causes of Hemorrhage

Bleeding occurred in three other cases, two of whom died. One of the latter (case 5) was a patient with chronic lymphatic leukemia who had been uneventfully biopsied twice previously, and whose prothrombin activity and platelet count were almost identical on the last occasion, when fatal hemorrhage occurred. She had received long-term chemotherapy, and there was considerable evidence of toxic liver damage at the time of death. A second patient, with carcinoma of the bladder (case 4), who had been on prolonged x-ray therapy with evidence of bone marrow depression, apparently developed a delayed hemorrhage 40 hours after the biopsy. The exact cause of death in this case is not entirely clear, since she had severe viral hepatitis and heart disease as well as her primary illness, but it is obvious that liver biopsy at least contributed to her death. A third patient with carcinoma

of the breast (case 1), treated with hormones and radioactive phosphorus, and evidencing severe and progressive bone marrow depression, bled massively but survived. All three of these patients had received prolonged therapy with agents toxic to the bone marrow, and exhibited bone marrow depression. Platelet counts and prothrombin activities were, however, within the lower limits of safety for biopsy as judged by our experience and that of others.[1, 12] In an attempt to evaluate these two factors as indicators to the danger of biopsy, platelet count and prothrombin times were checked in all uncomplicated cases of leukemia and lymphoma in this series. In the leukemias, there were four cases with platelet counts below 80,000, one of which was 42,000, and in the lymphoma group five cases with counts of 80,000 or less, the lowest being 68,000. Prothrombin activities were uniformly within safe range (55% or more of normal). Bleeding and clotting times as performed in the standard laboratory were felt to be too inaccurate to be valuable.

Discussion

In neoplastic disease, liver biopsy by the percutaneous route is a highly reliable means of demonstrating liver involvement by tumor, or by complicating benign disease. Both types of information may have the most profound influence on further management of the individual case. In many instances, biopsy may be a decisive factor when laboratory determinations are equivocal. The findings of unilateral left lobe involvement by biopsy and radioactive isotope liver scan technic in primary hepatoma, for example, may be the deciding factor in recommending attempted resection. Viral hepatitis, shown by liver biopsy during cancer therapy, may call for special consideration in adjustment of such therapy, as well as particularly careful measures for treatment of the hepatitis. Cirrhosis, the other most frequently noted complication, must be taken into special consideration if vigorous therapy is contemplated in the face of hypersplenism, anemia or malnutrition accompanying the underlying liver disease. Since it is a simple bedside procedure, with little discomfort to the patient, biopsy is especially useful in the evaluation of malignant neoplasm.

A recent paper [4] would indicate that biopsy in the presence of malignant hepatic neoplasm is especially dangerous, with a mortality of 12%. We are in agreement with others [1, 6] that the presence of tumor tissue alone is not necessarily an extra hazard. Cancer patients undergoing therapy, however, and those with massive bone marrow invasion by tumor, are definitely more liable to complications than are other groups. In only one instance in the present series did bleeding occur following biopsy of a liver involved by metastatic tumor (case 2). This patient also had myeloid metaplasia of the liver and massive tumor invasion of the bone marrow. Seventy-seven other biopsies in 65 patients with metastatic tumor of the liver did not bleed.

In this series there were six instances of major hemorrhage, with three

deaths, in 330 biopsies in a group of 280 patients. Our present experience may be contrasted with a previous one,[5] in which 630 biopsies were performed in a group of predominantly young and vigorous patients, most of whom had viral hepatitis, with no deaths, and only three instances of minor bleeding.

Analysis of the present group leads us to believe that percutaneous needle liver biopsy should be used with caution when (1) myeloid metaplasia is present or suspected, especially with evidence of bone marrow depression, or (2) when malignant tumor or leukemia has led to prolonged x-ray, isotope or chemotherapy treatment, with evidence of bone marrow damage. Each case of the latter group should be carefully evaluated, and biopsy withheld, especially if marrow depression is progressive and peripheral blood elements are unstable. With the present trends to vigorous cancer therapy, appreciation of these contraindications is particularly pertinent. As shown by case 5, fatal hemorrhage may occur in leukemia without apparent cause, although here, again, the patient had received prolonged chemotherapy, with clinical and laboratory evidence of toxic liver damage.

Summary

1. Evaluation of 330 percutaneous needle liver biopsies in 280 patients referred with proved or suspected malignant neoplasia showed 75.1% accuracy in detecting liver involvement in a group of proved malignant neoplasms.

2. Leukemic infiltration was found in eight of 12 cases of leukemia of all types; but in 30 cases of lymphomatous disease, liver involvement was discovered only five times. Hodgkin's disease was diagnosed unequivocally in no instance, although on autopsy, six out of 10 cases showed infiltration.

3. Six patients hemorrhaged following biopsy, with three deaths. Three of the six showed myeloid metaplasia of the liver, and the other three instances of bleeding occurred in patients with prolonged x-ray or chemotherapy, with evidence of bone marrow damage.

4. Leukemic patients may bleed following biopsy without apparent cause, but are especially liable to this complication when myeloid metaplasia of the liver is present, or when subjected to long-term chemotherapy.

5. Percutaneous needle biopsy of the liver is a valuable tool in the evaluation of malignant neoplastic disease. In our experience, complications have not been associated with simple tumor involvement of the liver, but have occurred in cases where there was definite evidence of bone marrow injury. Needle biopsy should be employed in confirmed neoplasia with caution when (1) myeloid metaplasia is present or suspected, especially with evidence of bone marrow depression, and (2) when there has been prolonged x-ray, radioactive isotope or chemotherapy treatment, with evidence of bone marrow damage.

SUMMARIO IN INTERLINGUA

Percutanee biopsia a agulia del hepate es un instrumento de valor in le diagnose de neoplasia primari o metastatic del hepate e in le evalutation de complicante morbo benigne in neoplasma maligne. Esseva effectuate 330 biopsias hepatic in 280 patientes presentate con neoplasia confirmate o suspecte. Le methodo monstrava un accuratia de 75.1% in deteger le affection del hepate in un gruppo de confirmate neoplasmas. Infiltrationes leucemic esseva trovate in 8 ex 12 casos de leucemia de omne typos, sed in 30 casos de morbo lymphomatose, un affection del hepate esseva discoperite solmente cinque vices. Morbo de Hodgkin non esseva diagnosticate, ben que in 6 ex 10 necropsias le presentia de infiltration esseva constatate.

In sex patientes, hemorrhagia sequeva le biopsia, con tres mortes. Tres del sex monstrava metaplasia myeloide del hepate. Le altere tres habeva recipite prolongate cursos de irradiation X o de chimotherapia, con evidentia de lesion del medulla ossee. Nulle complication esseva associate con simple neoplasia metastatic o con neoplasia primari del hepate, excepte in le presentia de definite indicios de lesion del medulla ossee. Biopsia a agulia debe esser usate con cirmumspection in casos de confirmate neoplasia si (1) metaplasia myeloide es presente o suspecte (specialmente con evidente depression del medulla ossee) e si (2) le patiente ha recipite prolongate cursos de therapia a radios X o a isotopos radioactive o de chimotherapia, con evidente lesion del medulla ossee.

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CASE REPORTS

ANAPHYLACTOID REACTION FOLLOWING ADMINISTRATION OF ONE MEPROBAMATE TABLET * †

By David M. Nevins, Captain, USAF (MC), *Columbus, Ohio*

Because of the countless number of drugs in use these days, we can expect more and more reports of bizarre side-effects, some quite serious and even life-threatening. The case that follows illustrates this point. The medication involved here is meprobamate,† a tranquilizer widely used and apparently relatively safe. Numerous minor reactions have been reported with meprobamate, but most of these were due to overdosage. Only a few cases have been recorded of hypotensive episodes following the administration of this drug.

Case Report

A 35 year old white male was admitted by ambulance to Lockbourne Air Force Base Hospital around 8:30 p.m. on September 27, 1959. Except for a mild upper respiratory infection which he had had the previous week, and for which he had taken aspirin and Chlor-trimeton, he had been in good health. He stated that he had used both of these drugs in the past with no harmful effects. Approximately six hours prior to admission he had taken one 400-mg. tablet of Miltown because of some pain and stiffness in the neck. Two hours later he developed a sudden onset of fever, shaking chills and malaise, followed by a severe erythema of his face and abdomen with pruritus. He denied ever having taken meprobamate previously or any similar preparation. There was no significant history of allergy.

On admission to the hospital, the patient appeared to be acutely ill with severe, shaking chills. The most striking finding was the intense rubor, similar in appearance to a bad sunburn. The skin was quite warm, and it was surprising that the rectal temperature was only 101.4° F. The admission blood pressure was 70/50 mm. of Hg, with a radial pulse of 140. In addition to the erythema, there was minimal bilateral periorbital edema. The pharynx was normal. A Rumpel-Leede test was positive. Routine laboratory work, including a complete blood count, hemoglobin, hematocrit, sedimentation rate, platelet count and urine analysis, was normal. An electrocardiogram revealed a sinus tachycardia, and a conventional posteroanterior film of the chest was normal. While being positioned for the x-ray, the patient had a brief episode of syncope.

Treatment consisted of Trendelenburg's position and keeping the patient as warm as possible with blankets. For the pruritus he received antihistamines. After it became evident that there was no improvement in his general condition, a drip of 1,000 c.c. of 5% glucose and saline with 10 mg. of Neo-synephrine was started. This also failed to raise his blood pressure. Soon afterwards he received 6 minims of aqueous epinephrine, 1:1,000 dilution. There was no change in his condition.

* Received for publication April 1, 1960.

† Meprobamate—Miltown (Wallace Laboratories, New Brunswick, New Jersey).

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Finally, 100 mg. of hydrocortisone were added to the intravenous solution, and within four hours there was a definite decrease in the intensity of the erythema, with marked relief from the pruritus, and the blood pressure rose to approximately 120/80 mm. of Hg. The following day the patient was placed on 25 mg. of prednisone; this was gradually decreased over the next few days. The only complaint the patient had was pruritus, which lasted approximately five days. His temperature returned to normal on the third hospital day.

Discussion

As mentioned previously, numerous accounts of meprobamate overdosages have been described, but very few of the anaphylactoid variety. Three cases of hypotension were reported in December, 1956.[1] In all three of the cases, however, the patients had taken at least four tablets. There was no effect on the pulse or temperature. Selling[2] in 1955 described certain minor side-effects noted in a study of 187 patients. One patient had two syncopal episodes, plus a temperature of 102° F., two and one-half hours after ingestion of two meprobamate tablets; a second patient developed urticaria; and a third, angioneurotic edema. These were after four and six days of meprobamate therapy, respectively. An extensive survey of meprobamate-idiosyncrasy by Charkes[3] revealed that one third of the 113 cases of idiosyncrasy began within eight hours after commencement of drug therapy. The earliest response appeared in 15 minutes.

Summary

A case is described of an anaphylactoid reaction following ingestion of one Miltown tablet. There was a dramatic response following intravenous hydrocortisone therapy.

Summario in Interlingua

Numerose reportos in le litteratura medical describe reactiones toxic causate per doses excessive de meprobamato. Tamen, relativemente pauc autores mentiona un reaction anaphylactoide.

Le patiente del hic reportate caso experientiava un satis sever collapso vascular pauc horas post le ingestion de un sol tabletta de meprobamato. Alleviamento esseva obtenite post le administration intravenose de hydrocortisona. Symptomas residue—prurito e erythema—persisteva durante plure dies.

Con le disponibilitate commercial de crescente numeros de drogas, le medico debe constantemente esser attente al possibilitate de reactiones toxic. Certes de istos es satis bizarre. Mesmo le plus innocente agente pote, in un subjecto particular, causar un serie si non de facto periculose situation. Un circumspecte interrogatorio del patiente con respecto a previemente notate idiosyncrasias pharmacodynamic deberea esser un parte essential del protocollo anamnestic.

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CHOLESTATIC JAUNDICE FROM TOLBUTAMIDE*

By R. William Baird, M.D., and John G. Hull, M.D., *Houston, Texas*

The list of chemicals capable of producing hepatic injury grows in disturbingly direct proportion to the number of drugs introduced into the pharmacy. The identification of these agents is of importance because the physician needs to balance the risk of any drug against its desired benefit with clearer eye and greater precision. Moreover, the perplexing problem of the differential diagnosis of jaundice is increased with each addition to the list.

This report concerns a patient with jaundice induced by tolbutamide. This relationship was demonstrated by the patient himself, quite unknowingly, when he performed a challenge test. As far as we know, this is the first indictment of tolbutamide as a cholestatic drug.

Case Report

A 57 year old machinist entered the hospital on December 7, 1959, for study of symptomless jaundice.

In June, 1959, he had consulted another physician, who told him he had diabetes mellitus and prescribed tolbutamide (Orinase), 3 gm. daily, and a low carbohydrate diet. Two weeks later his glycosuria disappeared and the drug was reduced to 1.5 gm. daily, and a few weeks later was discontinued by the physician. The patient, however, decided to use tolbutamide on a demand basis, and judged the dose by the degree of glycosuria. Using this technic, he took the drug irregularly through the month of August, and on September 2, 1959, jaundice appeared, clearly visible to himself and to his fellow workers. There were virtually no associated symptoms—no fever, no malaise, no anorexia, no abdominal pain. The urine was dark, the stool was light. The patient continued working and the jaundice gradually disappeared.

On November 16, 1960, the patient again noted glycosuria, took three tablets (1.5 gm.) of tolbutamide, and within two days observed reappearance of the jaundice. He continued to take this drug until the day of admission, while the jaundice continued unrelentingly. No other drugs were used, and there were no known chemical exposures. He had never used alcohol in large amounts. There had been a weight loss of 48 pounds during the preceding year, despite an excellent appetite. The family, occupational and social histories were not significant.

The past history revealed that the patient had been hospitalized elsewhere on September 25, 1957. At this time studies disclosed some impairment of liver function, manifested by a cephalin flocculation test of 2 plus in 24 hours and 3 plus in 48 hours, and a bromsulfalein retention of 50% at 30 minutes. The thymol turbidity, blood bilirubin and alkaline phosphatase and blood sugar values were normal at the time of this study.

One year later the thymol turbidity was 4.5 units, and the bromsulfalein retention was 5.8% at 45 minutes.

In November, 1958, the patient was again hospitalized, this time for treatment of bleeding from a diverticulum of the colon, which required one transfusion of

* Received for publication February 12, 1960.

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500 c.c. of whole blood. The following liver function studies were reported before the transfusion: blood bilirubin, 0.5 mg.; cephalin flocculation, 1 plus and 3 plus on one test, and 0 and 1 plus on another; thymol turbidity, 1.2 and 1.1 units; prothrombin time, 88%; bromsulfalein test, 13% retention at 45 minutes.

Physical Examination: The patient was an alert, jaundiced, well developed and well nourished male. No abnormalities of the head or neck were noted except for icteric sclerae. There was no lymphadenopathy. Examination of the heart and the lungs revealed no abnormality. The blood pressure was 130/80 mm. of Hg. The abdomen was flat. Neither the liver nor the spleen was palpable. No masses were felt in the abdomen, and the rectal examination was within normal limits.

Laboratory Studies in Hospital: Bilirubin, 7.7 mg.%; thymol turbidity, 0.8 unit; alkaline phosphatase, 9.7 Bodansky units; SGOT, 260. On December 21, 1959, the bilirubin was 6.0 mg.%.

An x-ray of the chest disclosed no significant abnormality. X-ray examination of the upper gastrointestinal tract was within normal limits.

An exploratory laparotomy was performed on the fourth hospital day. The surgical report follows: "The liver was moderately enlarged, smooth and moderately firm. The gall bladder and common duct were explored and no abnormalities were noted. The pancreas was normal."

Microscopic study of a liver biopsy was reported as follows: "The liver sections present a lobular pattern with some variation in the size of the lobules but the orientation of the central veins and portal triads is normal. Bile stasis, manifested by dark brown casts of inspissated bile, and granular brown bile pigment in the liver cells in the centers of the lobes, is present. Dense infiltrations of lymphocytes and a few eosinophiles are present in the periportal regions. There is some increase of periportal connective tissue which expands the relative size of the portal triad regions with corresponding reduction in size of the lobules. In the absence of biliary obstruction or disease it appears that the liver damage is due to drug toxicity."

Subsequent Course: The convalescence of the patient was rapid. He was discharged from the hospital on the sixteenth hospital day on a diabetic diet and 14 units of NPH insulin each morning. On this schedule there was no glycosuria. His weight increased six pounds in 20 days. The T tube was removed on December 30, 1959. Excellent healing occurred, and he returned to work on January 4, 1960. On January 2, 1960, the blood bilirubin was 2.2 mg.%; on January 8, 1960, it was 1.9 mg.%, and the stools and urine had returned to normal color. The final examination was performed on January 25, 1960, and the laboratory studies were as follows: cephalin flocculation, 3 plus; bilirubin, 1.6 mg./100 c.c. serum; thymol turbidity, 2.4 units; alkaline phosphatase, 5.0 Bodansky units.

Discussion

It seems evident that this represents an example of cholestatic jaundice induced by tolbutamide, probably grafted on an already disordered liver. The evidence for this is:

1. The time relationship between the use of tolbutamide and the appearance of jaundice.
2. The self-administered "challenge test."
3. The characteristically symptomless jaundice.
4. The improvement after discontinuance of the drug.
5. The laboratory findings consistent with stasis.
6. The microscopic picture of cholestasis in the liver biopsy.
7. The exclusion of biliary obstruction by surgical exploration.

Tolbutamide has a remarkably good record of safety. No reports of damage to the liver related to this drug were found. Jaundice has been reported in two other antidiabetic drugs, however; with chlorpropamide the rate was reported at 0.4%, and with metahexamide the rate was 0.8%.[1]

The problem of drug-induced hepatic injury is one of such magnitude that it has been recently proposed that patients receiving any of these drugs have a battery of liver tests initially, and twice weekly determinations of bromsulfalein, SGOT, alkaline phosphatase and perhaps bilirubin.[2]

We believe that this proposal is impractical because of the difficulties in patient coöperation, economics, and the limitation of laboratory facilities. It seems clear, however, that each patient should be told of the possibility of side-effects, and should be instructed in the observation of his own stool, urine and skin color.

Summary

A patient whose jaundice was produced by tolbutamide is reported. Tolbutamide must be added to the list of agents capable of producing cholestatic jaundice.

Acknowledgment

The assistance of the Pathology Department of the Hermann Hospital is gratefully acknowledged.

Summario in Interlingua

Le drogas capace a producer un vitio hepatic deveni de plus in plus numerose. Le uso de iste drogas pote complicar le diagnose differential de jalnessa. Iste reporto concerne le caso de un patiente con jalnessa producite per tolbutamido. Jalnessa sin symptomas appareva a duo occasiones in un masculo de 57 annos de etate post le uso de tolbutamido administrate pro leve diabete mellite. Un biopsia del hepate revelava stase biliar, un dense infiltration de lymphocytos, alicun eosinophilos in le regiones periportal, e un augmento in le tissu conjunctive periportal. Le exploration chirurgic revelava nulle obstruction del vias biliari.

Le jalnessa dispareva gradualmente, e le tests del function hepatic redeveniva normal post le suspension de tolbutamido.

Ab le puncto de vista de su innocentia medical, le "certificato de conducta" de tolbutamido es favorabile. Nulle previe reportos de jalnessa cholestatic causate per illo se trova in le litteratura. Tamen, como in le caso de multe altere drogas, omne patiente recipiente tolbutamido deberea esser informate del possibile effectos lateral del droga e del necessitate de reportar al medico omne alteration del color de pelle, fece, o urina.

Tolbutamido debe esser addite al lista del agentes capace a producer jalnessa cholestatic.

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UREMIA DUE TO RENAL LYMPHOMATOSIS *

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MALIGNANT lymphoma, also known as lymphosarcoma, has never been proved to exist as a primary lesion in the kidney. Davis and Olivetti [1] reported a case confined to the kidneys and the adrenal (chiefly cortex) and perirenal tissues, with one metastasis in the liver. They believed from the histologic characteristics that the lymphomatous process originated in the adrenal cortex and/or the periadrenal and perirenal adipose tissue. Since primary involvement of the kidney itself probably never occurs, Gibson [2] has suggested that the term "lymphosarcoma of the kidney" be replaced by the more nearly correct designation, "renal lymphomatosis."

The kidney is quite commonly involved secondarily by malignant lymphoma. This occurs either by metastasis or by direct invasion from neighboring foci of the disease. In one series of 1,047 consecutive autopsies,[3] 32 cases (3.1%) of malignant lymphoma were encountered. Renal involvement occurred in 17 (53%) of these 32 cases. The kidneys were involved less in reticulum cell sarcoma and Hodgkin's granuloma than in other types of lymphoma and leukemia. This is in contrast to the incidence of renal metastases in all malignant disease, reported in one series as 5.1%.[4]

Renal lymphomatosis may exist in the form of (1) minute foci scattered throughout the renal substance; (2) a diffuse infiltration or (3) a bulky, circumscribed tumor mass. The latter form is the most common.

In the case of renal lymphomatosis described in the literature,[5] some of the clinical manifestations have consisted of hematuria, pain in the renal area, unilateral or bilateral mass in the loin, oliguria, pyuria, uremia, loss of weight, malaise, poor appetite, fever, anemia, and edema of the lower extremities.

Local complications enumerated are severe renal hemorrhage and occasional ureteral obstructions with hydronephrosis. Since there is usually a widespread distribution of the disorder these patients may have all the symptoms of systemic malignant disease.

It has been stated that, although the renal cortex is usually involved first because of its greater vascularity, the glomeruli are the components most resistant to tumor. It is notable that despite overwhelming involvement by lymphoma, the functions of the kidney are rarely seriously compromised thereby. Thus, uremia is rare.[6] Death from progression of the generalized tumor process usually occurs prior to replacement of sufficient renal parenchyma to produce uremia.[7] It is extremely uncommon for patients with massive parenchymal lymphomatous infiltration in the kidney to develop an associated hypertension, even though one might anticipate an ischemic compression of small renal arteries and arterioles by the tumor.[8]

Renal calculi [9] due to elevation of serum uric acid are more frequent in patients with lymphoma and leukemia than in patients with other malignant

* Received for publication January 5, 1959.

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The opinions expressed are those of the author and do not necessarily reflect the views of the Department of the Navy.

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growths. With the exception of Hodgkin's disease, the incidence of renal calculi in patients with malignant lymphoma is as great or greater than that in leukemic patients.

It should be mentioned that a genetic component has been considered to be the cause of a higher incidence of lymphoma in some families.[10]

It is of value to make the diagnosis, since radiation and chemotherapy may improve the patient's renal status.

Case Report

A 68 year old Navy dependent was in good health until January, 1957, at which time she noticed a right supraclavicular mass. Biopsy taken at the U. S. Naval Hospital, Pensacola, Florida, was reported as "primary tumor of lymphoid tissue or lymphosarcoma."

One year later (January, 1958) the patient was re-admitted to the U. S. Naval Hospital at Pensacola with a one-month history of epigastric pain after meals. A periumbilical mass, 10 cm. in diameter, was found, seemingly in the subcutaneous tissues. The patient was given 200 kv. x-ray therapy over a 17-day period for a total dose of 2,700 r in air. There was a rapid diminution in the size of the mass. Three months later she developed herpes zoster over the fourth intercostal space anteriorly. For this she received 350 r in air to the low cervical and upper dorsal spine.

In March, 1958, the patient had a recurrence of her neck mass. Three months later she was admitted to the U. S. Naval Hospital, Portsmouth, Virginia. On physical examination she presented with a hard, movable mass 4 cm. in diameter in the right anterior inferior cervical region, and two small nodes in the left cervical chain. She also had a firm, movable midabdominal mass. The rest of the examination was normal. The laboratory studies were normal except for erythrocyte sedimentation rate of 35. It is of note that her blood urea nitrogen was 15.5, which is within normal range. (This was four months prior to her death.) Chest x-ray revealed tracheal deviation to the left, due probably to nodal involvement. The patient received 200 kv. x-ray therapy to the neck and abdomen for a total dose of 2,000 r in air.

On July 21, 1958, she was seen at the U. S. Naval Hospital, Newport, Rhode Island, for cough and abdominal cramps. At that time she had small, firm nodes in both cervical chains, and a 2 cm. midabdominal node. She had a radiodermatitis in the cervical region and periumbilically. It was felt that her cough was due to a radiotracheitis. She was presented to the Tumor Board. The members of the Board thought that the patient had already had sufficient irradiation and for the time being should have no more, because of her side-effects. She was therefore treated symptomatically. On August 1, 1958, she was admitted to the hospital for a period of one week. She was experiencing a change in the size and consistency of her stools, as well as abdominal cramps and knee pains. A fecal impaction found in the rectum was removed. Her abdominal mass had continued to diminish in size. X-rays of her chest, abdomen and knees were negative. She had a hematocrit of 35, hemoglobin of 11.9, erythrocyte sedimentation rate of 42, and white blood count of 4,900, with a normal differential count. Three urinalyses revealed persistent albuminuria ranging from 40 to 300 mg.%. Three stools were guaiac-negative. Liver function tests were normal.

On September 3, 1958, following a fall, the patient was re-admitted with severe weakness and an acute lumbosacral pain. On this admission it was noticed that she was disoriented at times and had extreme anorexia. She had to be fed by intravenous fluids, as she vigorously resisted the insertion of a nasogastric tube. X-rays of her

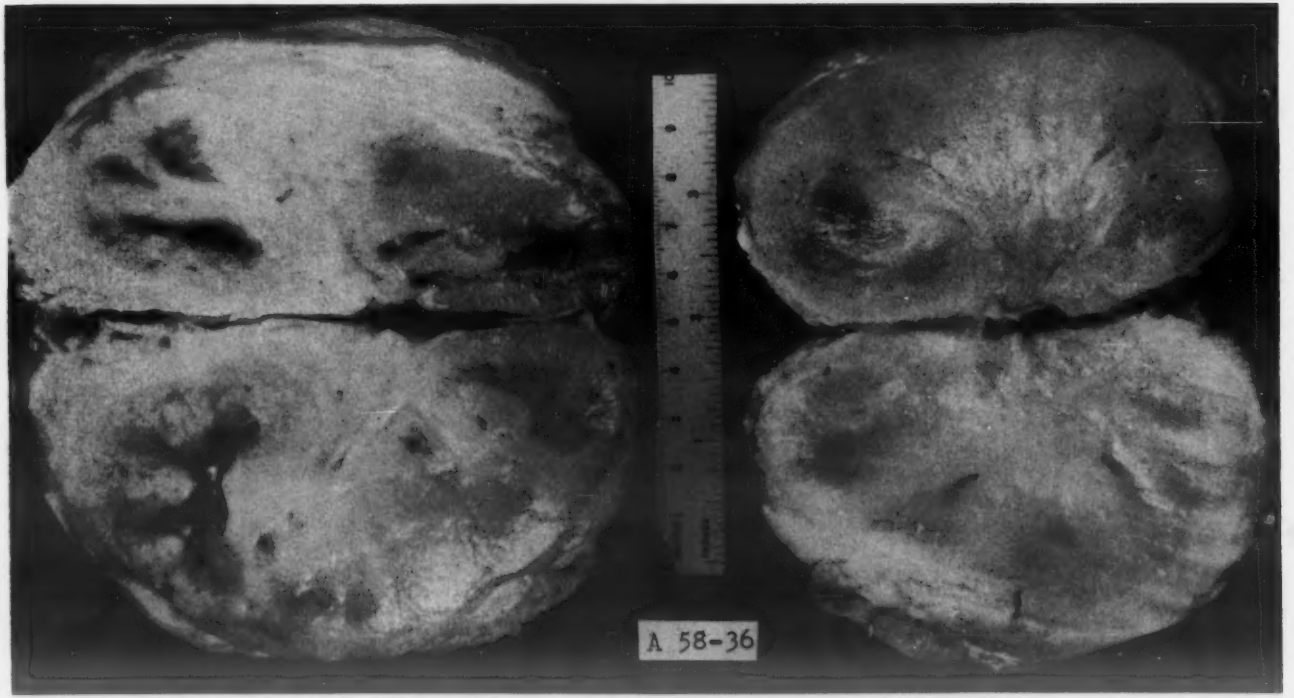


FIG. 1. Kidneys, gross sections. The right kidney weighed 420 gm., the left kidney, 310 gm. Both are seen to be diffusely infiltrated by gray-white glistening tumor. The malignant lymphoma has almost completely replaced the kidney bilaterally.

lumbosacral spine revealed severe osteoporosis but no tumor. X-ray revealed a "motheaten" appearance of the left femur head; this was highly suggestive of metastases. She had a hematocrit of 35, hemoglobin of 10.9, and normal white and differential counts. Urinalysis again showed persistent proteinuria, up to 100 mg.%. Clean catch urine revealed no growth. Despite good urine output, her blood urea nitrogen was now 51 mg.%. Her fasting blood sugar was 122 mg.% and her total protein 5.4 gm.%, with an albumin of 3.8 gm.%. She lapsed into coma over the next two days, and her blood urea nitrogen jumped to 83 mg.%, with a carbon dioxide of 11.2 mEq., a chloride of 89 mEq., a sodium of 144 mEq., and potassium of 3.9 mEq.

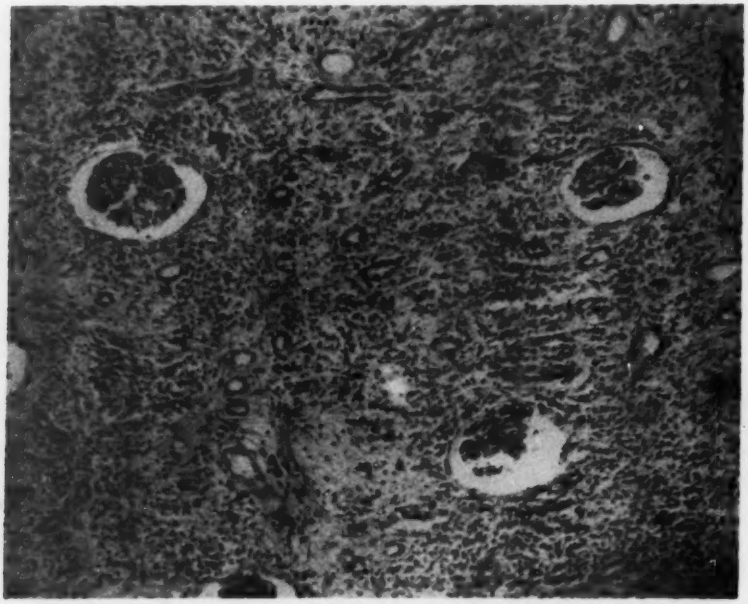


FIG. 2. Kidney, low power. Section showing marked obliteration of the kidney architecture and diffuse destruction and infiltration of the renal parenchyma. Some glomeruli are intact. (× 20.)

Forcing fluids brought her blood urea nitrogen down to 72 mg.% for a short time. She was started on 40 mg. per day of prednisolone, and even though there was no change in her blood urea nitrogen, she cleared mentally, regained her appetite, and was able to talk to her children. After 10 days on this drug she was well enough to go home. She did well at home on 20 mg. of prednisolone, but then deteriorated. She was re-admitted on October 3, 1958, extremely weak and disoriented, and died quietly during her sleep eight hours after admission.

At autopsy, moderate interstitial fibrosis was found in the heart. There was grade 2 atherosclerosis of the coronary arteries and aorta. There was diffuse enlargement of the peribronchial lymph nodes, which were gray-white and soft. The lungs were normal. There was a firm mass in the omentum, adherent to the anterior abdominal wall which measured 3 cm. in diameter and consisted of firm white tissue. There was general enlargement of the lymph nodes of the abdomen, especially around the abdominal aorta and the iliac arteries. All the nodes micro-

scopically were composed of large round or oval cells with vesiculated nuclei and prominent nucleoli. The liver presented atrophy of the left lobe. Microscopically, there was loss of hepatic cells in the left lobe. No tumor infiltration was noted in the liver or spleen. The pancreas, spleen and adrenal glands were normal. The gastrointestinal tract revealed diverticulosis of the colon.

The right kidney weighed 420 gm.; the left, 310 gm. The capsule did not strip, and appeared to be adherent to the kidney. It was thickened and gray-white. On section the kidneys appeared to be completely replaced bilaterally by firm, homogeneous gray-white and glistening tumor (figure 1). There was partial obliteration of one renal pelvis. The ureters appeared to be within normal limits. No renal calculi, hydronephrosis or pyonephrosis was identified.

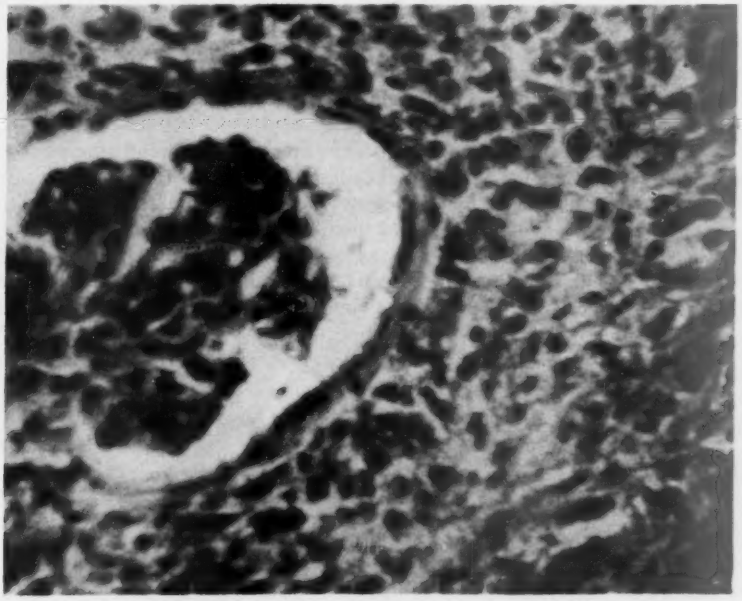


FIG. 3. Kidney, high power. A normal glomerulus is seen surrounded by tumor cells that are variable in size and shape from spindle to round. (× 81.)

On microscopic examination the tumor cells were variable in size, and were from spindle to round and oval in shape. The cytoplasm of the cells appeared to be delicate and fibrillar; the nuclei had a somewhat vesicular appearance. There were marked diffuse destruction and infiltration through all sections of both kidneys (figures 1, 2 and 3).

The final diagnosis was malignant lymphoma, lymphoblastic type, generalized, with extensive bilateral kidney infiltration by tumor, with death due to uremia.

COMMENT

This tumor was classified as a lymphoblastic lymphoma, using the classification outlined by Carter.[11] The histologic picture is monotonously uniform, but the majority of cells comprising the tumor are lymphoblasts. Leukemia [12] occurs

in approximately 38% of the cases and, when present, is usually of the acute variety. In this case there were no signs of leukemia in the peripheral blood.

The tumor invasion of the kidney was of the diffuse infiltration variety, which is the rarest type. The patient had no signs of renal stones or of hydronephrosis or pyonephrosis which could have added to the retention of nitrogenous wastes. The left lobe of the liver was atrophic, as it was in the beam of the periumbilical irradiation given, but it was felt improbable that the right lobe of the liver or spleen could have received enough spray irradiation to have caused the disappearance of tumor infiltrates. Though both spleen and liver [13] are commonly seats of lesion in malignant lymphoma, the patient's liver and spleen were free of tumor at autopsy.

Patients with lymphoma seem to be particularly susceptible to herpes zoster. The lesions tend to be severe.[14] This was true of this case.

Intravenous pyelography was not performed because of the patient's uremia and the severity of her condition. She was given neither nitrogen mustard nor x-ray therapy on her last admission, because of the side-effects experienced after a full course of irradiation two months prior to her last hospital admission. It is of interest that symptoms of uremia manifested themselves only three weeks prior to her death, and that at that time she had an elevated blood urea nitrogen. It is not known how long her blood urea nitrogen had been increasing, except that it had been normal four months prior to her death. She came out of coma and became totally rational under prednisolone therapy. This was a dramatic but short-term symptomatic improvement. There was no coincident improvement, however, in renal function.

ACTH and cortisone have been described as causing both a reduction in the size of lymphomatous tumors and an amelioration of symptoms.[15] They have also been beneficial in the treatment of hemolytic anemia due to lymphoma, which this patient did not have. Remissions have been described as being brief, as they were in this case.

Summary

A case is presented of uremia following extensive bilateral diffuse infiltration of the kidneys by malignant lymphoma. There were neither renal stones nor obstruction of the renal pelvis or ureters to account for the uremia. At autopsy the liver and spleen were not infiltrated by tumor. Despite massive infiltration and replacement of renal tissue, there was a relatively late appearance of uremic symptomatology. Marked but brief symptomatic improvement occurred with steroid therapy. It is of definite value to think of this diagnosis, since the patient's general disease and renal status may be improved by appropriate roentgen and chemotherapy.

Summario in Interlingua

Es presentate un caso de uremia observate in un femina de 68 annos de etate post un extense infiltration diffuse de ambe renes per un lymphoma maligne. Le patiente habeva notate le morbo initialmente in le forma de allargate nodos dextero-supraclavicular un anno e novem menses ante su morte. Il esseva cognoscite que illa habeva habite normal nivellos de nitrogeno del urea del sanguine quatro menses

ante su morte. Illa deveniva comatose le prime vice tres septimanas ante su morte. A ille tempore le nitrogeno del urea sanguinee amontava a 83 mg%. Le tumor esseva classificate como lymphoma lymphoblastic. In le renes le tumor esseva del typo infiltrative diffuse, lo que es le forma le plus rar de affection lymphomatose del ren.

Es opinate que lymphoma primari del ren probabilemente non occurre del toto. Il ha essite notate que—in despecto del massive affection per lymphoma—le functiones del ren es rarmente compromittite a grados seriose. Assi le presentia de uremia es rar. Le patiente del presente reporto exhibiva nulle signo de calculos renal o de hydronephrosis o pyonephrosis que haberea potite accentuar le retention de deciduos nitrogenose. Ben que splen e hepate es communmente sitos de lesiones in lymphoma maligne, in le presente caso le necropsia revelava nulle tumor in ille duo organos. Le patiente resurgeva ab le coma e redeveniva completemente rational sub le effecto de therapia a prednisolona. Iste melioration symptomatic esseva dramatic sed de breve duration, de accordo con publicate observationes in casos de lymphoma in que remissiones esseva effectuate per medio de steroide le quales esseva definite sed breve. Nulle melioration del function renal esseva effectuate per le steroide. Il es definitemente de valor pensar in iste connexion a un diagnose de affection renal per lymphoma maligne, proque le morbo general e le stato renal de tal patientes pote esser meliorate per formas appropriate de roentgenotherapia e de chimotherapia.

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DIAGNOSIS OF *BRUCELLA MELITENSIS* INFECTION BY PERCUTANEOUS NEEDLE BIOPSY OF THE LIVER *

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THE only absolute confirmation of the diagnosis of brucellosis is the isolation of *Brucella* organisms from the patient. *Brucella* organisms tend to localize in sites where there are large amounts of reticuloendothelial tissue.[1] Hepatic involvement in brucellosis has been known since the original description of undulant fever as a disease entity by Marston in 1859.[2] Needle biopsy has been used to obtain *Brucella abortus* after blood cultures were negative.[2, 3] Such a report from our own hospital [3] stimulated us to make an attempt at confirmation of a suspected case of brucellosis by percutaneous needle biopsy of the liver. The diagnosis of acute brucellosis by culture of liver biopsy material has been recorded only infrequently. Isolation specifically of *Brucella melitensis* is reported for the first time to our knowledge in this paper.

CASE REPORT

A 25 year old Negro male butcher had been well until two weeks prior to admission, at which time he had begun to feel weak and sluggish, and was sent home from work with a temperature of 101° F. The fever persisted, and he developed diaphoresis and chills. During the week prior to admission there were several episodes of nausea and vomiting. The urine was reported to be "darker than normal," but there was no change in the color of the stools. At no time were there complaints of diarrhea, constipation, pain, flatulence, eructation, melena, hematuria or hematemesis. The patient had received no injections in the last year, and denied recent drug or alcohol intake, animal bites, or contact with rodents. However, he did recall that a jagged piece of hog bone had caused an abrasion on his left forearm two weeks before the onset of symptoms. His occupation was that of a butcher in a slaughterhouse, mainly handling hogs. His personal and past history was otherwise noncontributory.

Physical examination on admission revealed a well developed, well nourished Negro male in no acute distress but showing evidence of recent illness. The pertinent findings consisted of the following: blood pressure, 120/80 mm. Hg; pulse rate, 88 per minute; temperature, 102° F. A few small nontender, discrete lateral cervical nodes were present. The chest, heart and lung examinations were noncontributory. The abdomen was soft. There was tenderness in the right upper quadrant. The liver edge was palpated two fingerbreadths below the right costal margin; the edge was firm and not tender. The spleen was not palpable. The remainder of the examination was within normal limits.

The laboratory findings of note were as follows: The red blood count and hemoglobin were within normal limits. There was a relative lymphocytosis of 51% and 76% on two occasions, with accompanying white blood counts of approximately 6,000. Lupus erythematosus cells and sickling of red cells were not found. Blood smears were negative for malaria parasites. Urine urobilinogen of 1:200 was noted. Pertinent chemical findings consisted of a serum glutamic oxalacetic transaminase

* Received for publication January 13, 1959.
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ranging from 35 to 54 units, and a serum glutamic pyruvic transaminase from 50 to 130 units. The total protein was 7.4 gm.%, with a reversal of the albumin/globulin ratio (3.2/4.2). The bromsulfalein test indicated 16% retention. The van den Bergh reaction was negative. *Brucella* agglutination titers of over 1:640 were found on two occasions. Cold agglutinins and agglutinins for typhoid O and H antigens and *Pasteurella tularensis* were not elevated. Seven venous blood cultures and several stool and urine cultures were negative for *Brucellae*. Tests for tuberculosis using purified protein derivative (PPD) in two strengths were negative, as were skin tests for coccidioidomycosis, histoplasmosis and blastomycosis.

A liver biopsy was performed on the fifth hospital day. After five weeks, a culture from this tissue grew *B. melitensis*.

Just after the biopsy was performed the patient, who had been spiking temperatures up to 105° F., was started on 1 gm. of intravenous chlortetracycline per day. Within 48 hours the temperature had become normal, and it remained so for the length of hospitalization.

The patient appears clinically well after five months. Laboratory results indicate a red blood count of 3.4 million and a hemoglobin of 14.5 gm. The white blood count is 6,600, with a normal differential. The sedimentation rate is within normal limits. The *Brucella* agglutination titer is 1:80.

Discussion

Brucellosis is found chiefly among workers whose occupation brings them into close contact with animals at the time of slaughter.[4] The disease is spread by direct contact with animals and by the use of raw dairy products from infected cows. Brucellosis due to *B. melitensis* is usually found in handlers of sheep and goats,[5] but the organism has been transmitted from hogs,[5] as evidently occurred in this case. There is no known episode of person-to-person contact. The male population is infected five times as frequently as is the female, probably because of the greater number of male farm and dairy workers. Most cases occur in the summer months.

The symptoms of chills, fever and sweating, weakness, malaise, headache, joint pains, anorexia and weight loss are well known. Findings of rash, nosebleed, glandular swellings and nasal ulcerations have also been recorded.[5] The rash, macular in character, resembles that seen in streptococcal septicemia.

Our patient developed a relative lymphocytosis and relative leukopenia. This has been reported frequently in brucellosis. An increased serum globulin level and a reversal of the A/G ratio have also been reported frequently. Of course, the *Brucella* agglutination titer of over 1:640 on two occasions made us more certain of our clinical diagnosis and prompted us to consider liver biopsy. A *Brucella agglutination* titer of over 1:100 is strongly suggestive of either previous or present infection with *Brucellae*, though it may be due to cross agglutination with *Pasteurella tularensis*. However, an agglutination titer of over 1:320 must be considered to be specific for brucellosis, and almost always means present infection.[1]

Summary

Our case presented a rather typical onset of the acute or septicemic type of brucellosis, characteristic of *B. melitensis* infection.[5] As is a common occurrence, no organism could be found in spite of repeated venous blood cultures. Our ex-

perience reëmphasizes the feasibility of obtaining positive cultures by means of percutaneous needle biopsy of the liver.

To the best of our knowledge, there has been no previous report of the isolation of *B. melitensis* from tissue obtained by percutaneous needle biopsy of the liver.

The medicolegal implications of this case are apparent, since introduction of a disease-producing organism could have taken place through traumatic exposure. Precise identification of the etiologic organism is therefore important.

ACKNOWLEDGMENT

We wish to thank Miss C. Luftig for aid in preparing this paper.

SUMMARIO IN INTERLINGUA

Le sol confirmation absolute de brucellosis es le isolation de organismos de Brucella ab le patiente. Iste organismos ha le tendentia de localisar se in sitos characterisate per le presentia de grande quantitates de tissu reticuloendothelial. Le presentia de un affection hepatic in brucellosis es cognoscite depost le tempore del description original de febre undulante como un entitate pathologic per Marston in 1859. Biopsias a agulia ha previemente essite utilisate pro obtener organismos de *Br. abortus* post que culturas de sanguine se habeva monstrate negative, sed le diagnose de brucellosis acute per medio del cultura de specimens bioptic ab le hepate es mentionate infrequentemente in le litteratura. Le isolation, per ille methodo, de *Br. melitensis* in particular es hic reportate, in tanto que nos lo sape, pro le prime vice.

Le patiente esseva un carnero de 25 annos de etate, empleate in un abattitorio que esseva interessate primarimente in porcos. Duo septimanas ante su hospitalisation ille disveloppava debilitate e malaise, sequite un septimana plus tarde per febre e algor. Le constatationes pertinente del examine physic esseva lymphadenopathia e hepatomegalia. Esseva trovate lymphocytosis relative, anormalitate del tests de function hepatic, e un reversion del proportion inter albumina e globulina. Studios serologic produceva titros de agglutination brucellic de plus que 1:640. Septe culturas venose e plure culturas fecal e urinari esseva negative pro *Brucella*.

Biopsia hepatic esseva effectuate. Post cinque septimanas, un cultura de *Br. melitensis* esseva confirmate. Plus tarde, le patiente respondeva promptemente a doses diurne de 1 g de chlortetracyclina per via intravenose. Hodie, post cinque menses, le patiente se porta clinicamente ben.

Le caso signala de novo le practicabilitate de obtener positive culturas de *Brucella* per medio de percutanee biopsias del hepate.

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OBSERVATIONS ON A CASE OF ERYTHREMIC MYELOSIS *

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WHILE the nature of erythremic myelosis (di Guglielmo's disease) remains controversial, it is not surprising that the diagnosis may give rise to considerable difficulty. The differentiation from various forms of hemolytic anemia and from severe cases of pernicious anemia presents well recognized difficulties. The application of diagnostic aids of more recent development has been limited by the rarity of the disease; this limitation would seem to warrant the presentation of a case of erythremic myelosis where the red cell survival and serum vitamin B_{12} content were estimated, and a cytochemical abnormality in the marrow normoblasts, of possible diagnostic value, was demonstrated. The termination as acute monoblastic leukemia adds a further case to the now well recognized relationship between di Guglielmo's disease and the acute leukemias.

CASE REPORT

Clinical History: A Bantu (Negro) male, age 48, a delivery man, was admitted to hospital on October 8, 1956. The present illness had started two months prior to admission, when progressive tiredness was noticed. No spontaneous bruising or bleeding was reported.

Examination showed marked pallor of the conjunctivae and mucous membranes. There was no evidence of jaundice, purpuric spots, bruising of the skin, lymphadenopathy, hepatosplenomegaly or bone tenderness. The retinae showed pallor of both discs and flame-shaped hemorrhages. The cardiovascular and respiratory systems were normal. Radiologic study of the skull, chest, vertebrae, pelvis, long bones and hands failed to reveal any abnormality.

Laboratory Findings: Blood count on the day after admission showed hemoglobin, 7.7 gm. per 100 ml.; leukocytes, 2.4 thousand per cubic millimeter (neutrophils, 19%; monocytes, 2%; lymphocytes, 72%; eosinophils, 5%; plasma cells, 2%), with recticulocytes, 1%, and normoblasts, 120 per cubic millimeter. No platelets were observed on the smears. The packed cell volume was 22%, and the mean corpuscular hemoglobin concentration, 35%.

Marrow was aspirated from the sternum. The specimen (table 1) was hypercellular, due to marked erythroid hyperplasia, but the erythroid elements showed gross abnormalities. The normoblasts were largely atypical, with nuclei resembling those of reticulum cells and occasional megaloblast-like forms (figure 1). Numerous immature multinucleated red cell precursors of bizarre morphology were noted, and there were many mitotic figures, some abnormal. Myeloid elements and megakaryocytes were scanty. The picture was considered to be that of erythremic myelosis; the clinical features and peripheral blood findings suggested a subacute form.

Periodic acid-Schiff staining of the marrow films revealed the presence of numerous large para-aminosalicylic acid (PAS)-positive granules in the cytoplasm of many of the normoblasts (figure 2).

* Received for publication January 6, 1959.
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Requests for reprints should be addressed to The Librarian, South African Institute for Medical Research, P.O. Box 1038, Johannesburg, South Africa.

TABLE 1

Marrow Differential Counts

Cell Type	October 13, 1956	January 7, 1957
Reticulum cells	4.0%	
"Blast cells"	0.2%	85%
Promyelocytes	0.2%	
Myelocytes: neutrophil	4.6%	3%
eosinophil	0.4%	
Metamyelocytes	0.2%	
Staff cells	2.4%	
Polymorphonuclears: neutrophil	0.6%	
eosinophil	0.2%	
Lymphocytes	1.0%	9%
Plasma cells	0.6%	
Pronormoblasts	10.4%	
Normoblasts: basophilic	9.2%	1%
polychromatic	60.0%	2%
pyknotic	6.0%	
Myeloid-erythroid ratio	1:9.8	

The serum bilirubin was 0.8 mg. per 100 ml., and there was no excessive urobilin in the urine. Sickling could not be demonstrated, and the osmotic fragility of the red cells was normal. The direct Coombs' test was negative, and abnormal antibodies could not be demonstrated. The Donath-Landsteiner and Ham's acid-serum tests were negative. Cold agglutinins were not present. Paper electrophoresis of hemoglobin

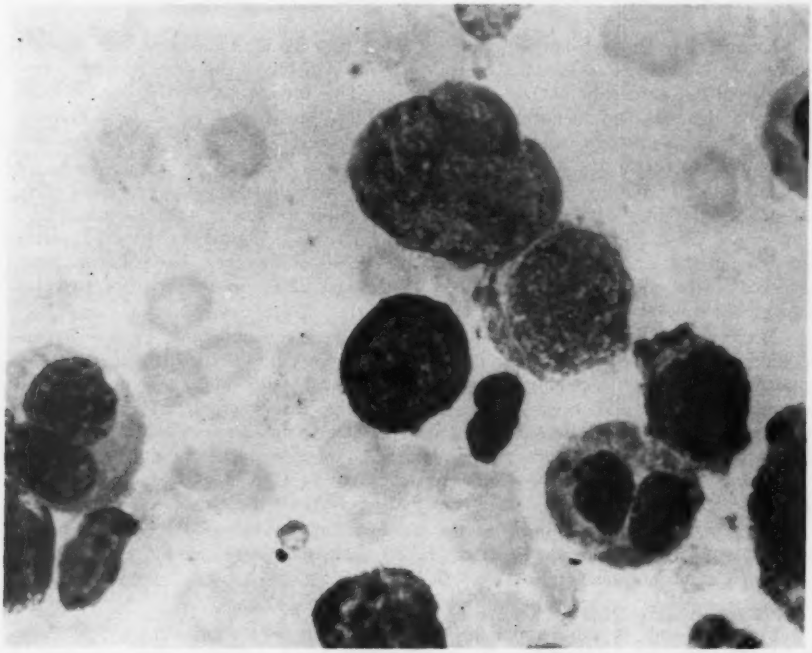


FIG. 1. Marrow puncture: atypical normoblasts, some with nuclei resembling reticulum-cell nuclei, and megaloblast-like forms. A Howell-Jolly body is present in a binucleate cell.

in a Veronal buffer (pH, 8.6) showed a single component with mobility of hemoglobin A. Alkali-resistant hemoglobin was 0.8%, and solubility in 2.58 M. phosphate buffer (pH, 6.9, 25° C.) was 1.3 gm. per liter. A red cell survival study using radioactive chromium-51 showed a mean cell life [2] of 17 days.

Gastric analysis revealed the presence of a normal amount of hydrochloric acid. Microbiologic assay of vitamin B_{12} in the serum, using *Euglena gracilis* as test organism (carried out by Dr. D. L. Mollin, at Post-graduate Medical School, London), showed a content of 575 $\mu\mu$ per milliliter.

Further Progress: On October 12, 1956, four days after admission, therapy with prednisone, 6 mg. daily, was started, and was continued for 17 days without any effect

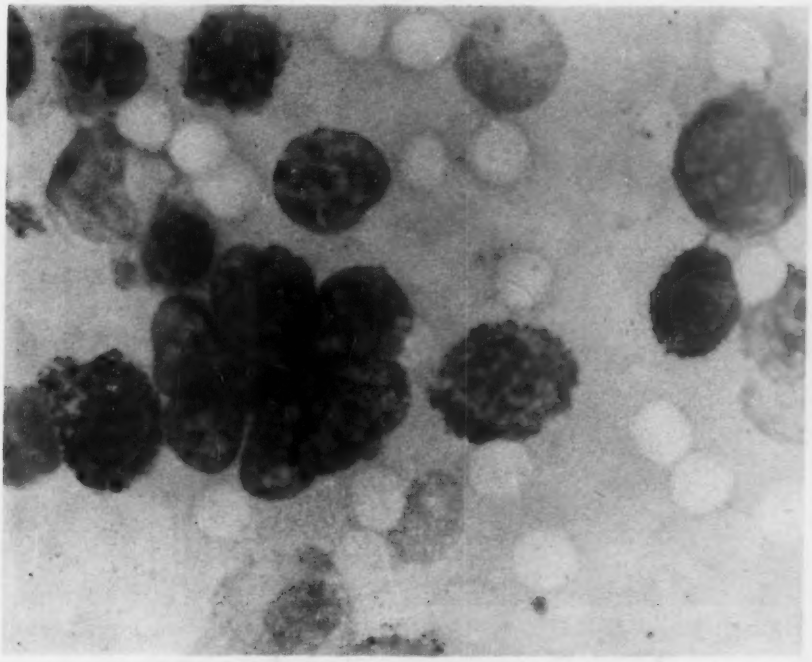


FIG. 2. Marrow puncture: PAS-positive granules in the cytoplasm of normoblasts.

on the peripheral blood picture, the blood remaining pancytopenic throughout. On October 29, therapy with vitamin B_{12}, 100 μg. daily by intramuscular injection, and folic acid, 30 mg. daily by mouth, was started. On October 31, 2 L. of blood were transfused. The therapy with vitamin B_{12} and folic acid over a period of 14 days failed to influence the peripheral blood picture, and repeat marrow examination on November 11, 1956, failed to reveal any significant change. On November 8 there was a bleeding episode from the gums; the bleeding time was 15 minutes, and the capillary fragility test was positive. Bleeding tendency was apparently more severe than when the patient was receiving prednisone, and therapy with prednisone, 60 mg. daily, was therefore reinstituted on November 13. After a further blood transfusion of 1 L. on November 26 the patient was discharged, maintained on 30 mg. of prednisone daily. The blood picture still showed a pancytopenia. During the stay in

hospital the largest number of normoblasts present in the peripheral blood was 595 per cubic millimeter.

On December 20, 1956, three weeks later, the patient was re-admitted, complaining of tiredness and bleeding from his gums. Hemorrhagic bullae were present in the mouth, and there was generalized purpura. The peripheral blood showed a pancytopenia, but an additional feature was the appearance of a small number (7%) of "blast cells." One liter of blood was transfused, and the prednisone was increased to 60 mg. daily.

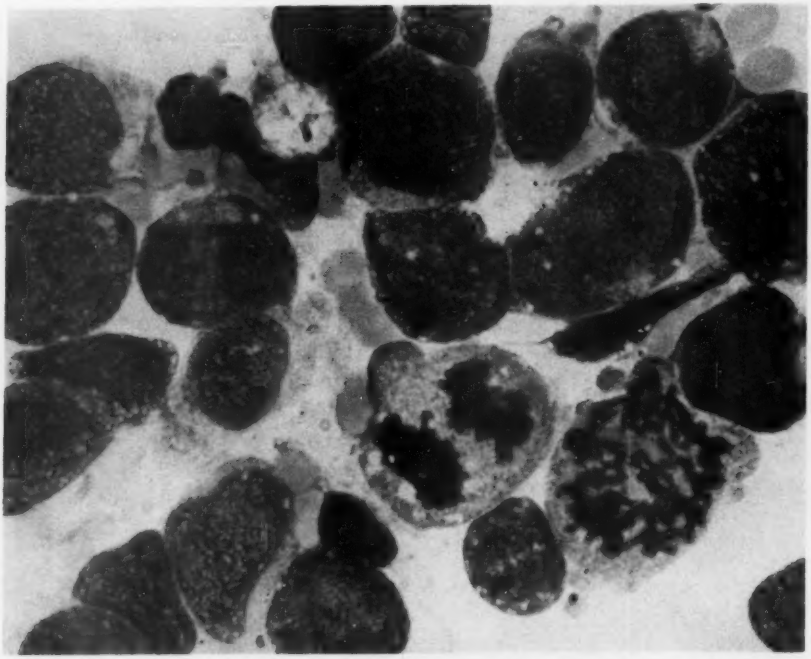


FIG. 3. Marrow puncture: replacement by blast cells, some with convoluted nuclei. Two mitotic figures are present.

Two weeks later (five months after the onset of symptoms) the blood picture had completely changed, in that the leukocyte count had risen to 19.2 thousand per cubic millimeter, of which 77% were "blast cells." Sternal puncture (table 1) now showed the marrow to be virtually completely replaced by primitive blast cells, somewhat larger than myeloblasts, and some with convoluted nuclei (figure 3). A feature was the very marked degree of erythrophagocytosis by the blast cells (figure 4). The picture was now that of an acute monoblastic leukemia. There was no lymphadenopathy, but the tip of the spleen was palpable. Therapy with 6-mercaptopurine (1 mg. per pound of body weight per day) was now added to the prednisone, but the patient died the next day (January 8, 1957) following a sudden hematemesis and melena.

Necropsy: Only the significant findings are reported. Autopsy was carried out 33 hours after death. Numerous small purpuric spots were scattered over the skin

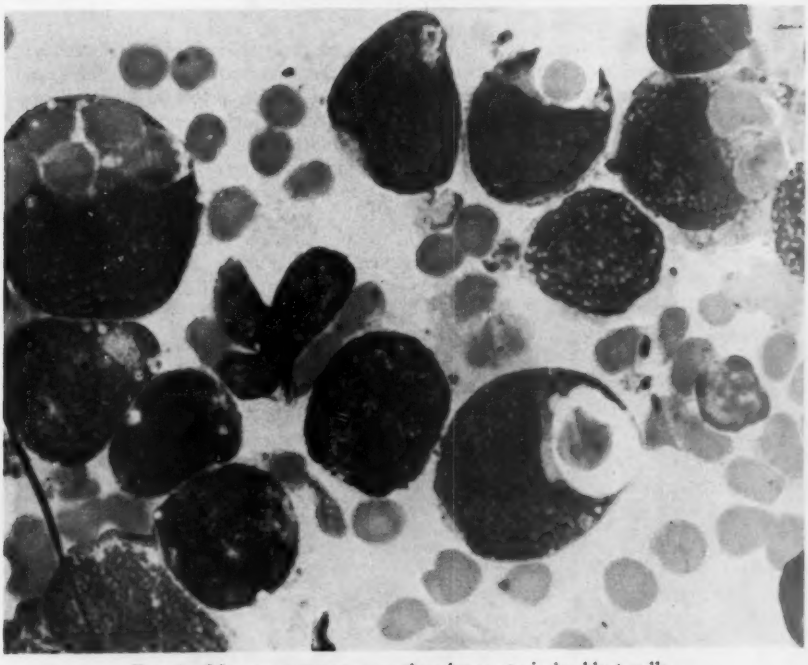


FIG. 4. Marrow puncture: erythrophagocytosis by blast cells.

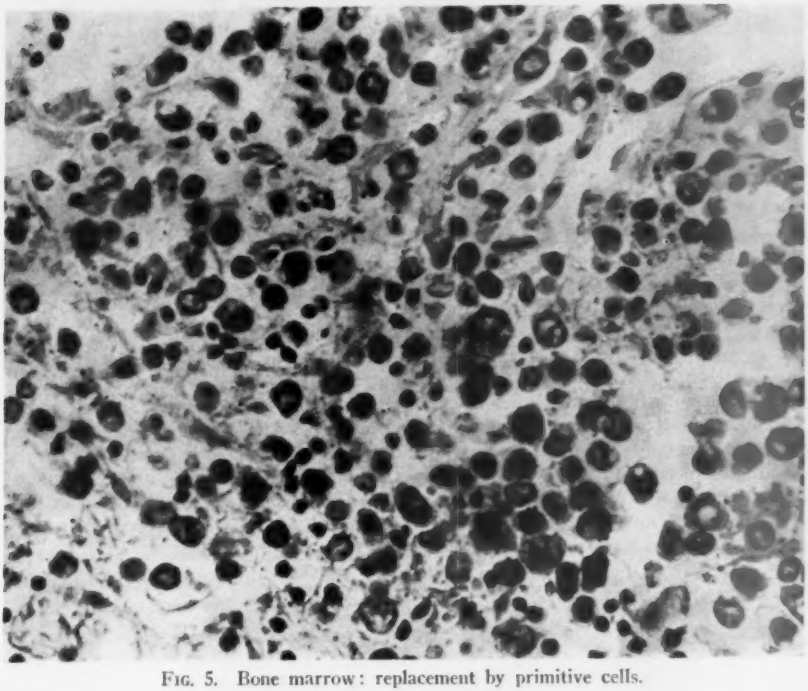


FIG. 5. Bone marrow: replacement by primitive cells.

of the trunk, arms and legs, and the mouth showed the presence of a hemorrhagic bullus. The stomach and intestines contained a large quantity of blackish fluid, and the mucosal surface showed the presence of numerous minute petechial hemorrhages. The liver (2,200 gm.) and spleen (617 gm.) on section presented a homogeneous, smooth appearance, suggesting diffuse leukemic infiltration. The tracheobronchial, hilar, mesenteric, axillary, cervical and inguinal lymph nodes were not enlarged and on section showed no macroscopic lesion. The femoral, vertebral and sternal marrow was uniformly pinkish gray in color, and in parts was soft and diffluent in consistency, resembling pus. The adrenal glands showed the presence of soft, pinkish gray tissue replacing the medulla in parts, suggesting leukemic infiltration.

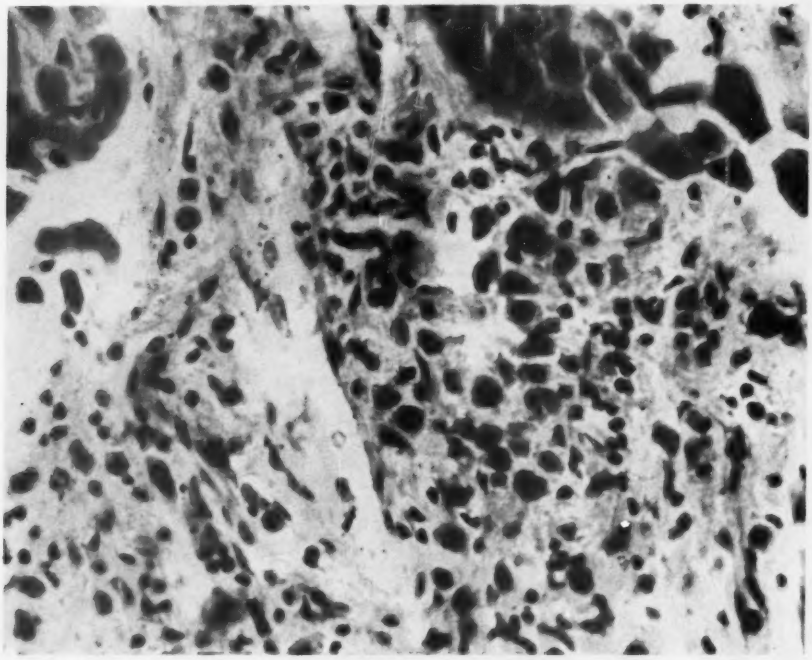


FIG. 6. Liver: infiltration in the portal tracts.

Histology: The spleen showed extensive infiltration of the pulp by large atypical cells, with oval or irregularly shaped vesicular nuclei and abundant basophilic cytoplasm. A few binucleate cells were present. Apart from a few groups of lymphocytes representing the remnants of malpighian corpuscles, these cells had completely replaced the normal splenic tissue. The vertebral and femoral marrow showed complete replacement of normal marrow by primitive cells (figure 5), similar to those seen in the spleen. The liver showed numerous large atypical cells, similar to those seen in the spleen and marrow, present in the portal tracts (figure 6), and the kidney showed well marked focal infiltration by primitive cells, similar to those noted in the bone marrow. Small areas of infiltration by primitive cells were present in the suprarenal glands. The autopsy diagnosis was:

1. Acute leukemia with infiltration of liver, spleen, kidneys and suprarenal glands.
2. Gastrointestinal hemorrhage.

Discussion

One of the greatest problems in the diagnosis of erythremic myelosis and erythroleukemia is the differentiation from the various forms of hemolytic anemia, especially early in the course of the disease. In the present case, all investigations aimed at diagnosing or excluding the more usual forms of hemolytic anemia were negative. The problem has become considerably more complicated following the recognition that the anemia accompanying malignant blood diseases is very often hemolytic in nature, the hemolysis not being of the overt type, and generally established only by demonstration of diminished red cell survival. A hemolytic component in the anemia accompanying erythremic myelosis has long been suspected; Schwartz and Critchlow,[5] in their review of the disease, cited four cases with strong evidence of accelerated blood destruction. Di Guglielmo [4] stated that, owing to the presence of fragile erythrocytes, more easily destroyed than normal, the disease frequently assumes the aspects of hemolytic anemia, with extreme proliferation of the reticuloendothelial system and phagocytosis of the erythrocytes.

In the investigation of the present case, a red cell survival study was carried out to establish whether this could distinguish a primary hemolytic anemia from the anemia accompanying erythremic myelosis, and to determine if red cell survival is indeed shortened in this disease. The results indicate a very markedly diminished red cell survival, confirming that there may be a marked hemolytic factor in the genesis of the anemia accompanying erythremic myelosis. Estimation of red cell survival will not necessarily aid in distinguishing erythremic myelosis from bizarre forms of hemolytic anemia. An extreme degree of erythrophagocytosis was noted at the time of the patient's final admission; however, at the time of the red cell survival study, erythrophagocytosis was not a feature shown by the marrow punctures. It would appear that the hemolytic component which may be present is not necessarily due to the severe erythrophagocytosis by reticuloendothelial elements.

A further problem in the diagnosis of erythremic myelosis is the resemblance which the disease may have to pernicious anemia. The marked maturation arrest in the marrow, associated with megaloblast-like cells, may well give rise to confusion; in the case reported by Stodtmeister,[6] cells indistinguishable from the megaloblasts of pernicious anemia were present. The finding of a normal vitamin B_{12} content in the serum of the present case indicates that this investigation may be of value in distinguishing pernicious anemia from erythremic myelosis; the serum vitamin B_{12} content in pernicious anemia in relapse is invariably low.

The histochemical abnormality in the staining of the normoblasts in erythremic myelosis is of interest. The Hotchkiss reaction which was suggested as a possible differentiating feature between thalassemia major and erythremic myelosis [3] cannot distinguish the two conditions. This cytochemical abnormality, which was not found in other forms of malignant blood diseases,[1, 3] may possibly be of some diagnostic value.

Summary

A case of subacute erythremic myelosis terminating as acute monoblastic leukemia is presented.

Estimation of red cell survival by means of radioactive chromium 51 showed a markedly increased rate of destruction of the red cells.

Assay of vitamin B_{12} in the serum was within normal limits.

A cytochemical abnormality in the marrow normoblasts was demonstrated with the periodic acid-Schiff stain.

ACKNOWLEDGMENTS

We wish to thank Professor G. di Guglielmo for his kindness in reporting on the bone marrow films; Dr. D. L. Mollin for the vitamin B_{12} assay; Dr. I. W. Simson for the post-mortem report; Dr. C. J. Anderson for the hemoglobin studies; Professor J. F. Murray and Dr. V. H. Wilson, Dr. R. Cassel and Dr. H. B. W. Greig for their assistance, and Mr. M. Ulrich for the photographs.

SUMMARIO IN INTERLINGUA

Un adulto bantu se presentava al hospital con le gravamine de fatiga. Le examine physic revelava pallor e hemorrhagias fundal. Le numeration del cellulas sanguinee indicava sever pancytopenia, con normoblastos amontante a 120 per mm^3. Le medulla sternal monstrava grados marcate de hyperplasia erythroide, sed le elementos erythroide esseva grossiermente anormal. Le tableau congrueva con myelosis erythremic. Tincturation de frottis de medulla con acido periodic de Schiff revelava numerose granulos a positivitate pro acido para-aminosalicylic in le cytoplasma del normoblastos. Un studio del longevitate erythrocytic (utilisante Cr^{51}) produceva un valor medie de 17 dies. Le contento seral de vitamina B_{12} esseva 575 $\mu\mu$g per ml.

Therapia con vitamina B_{12}, acido folic, e prednisona esseva sin effecto super le hematogramma, sed le tendentia sanguinatori esseva plus sever quando le prednisona esseva suspendite. Dece septimanas post le admission al hospital un certe numero de blastocytos esseva notate in le sanguine peripheric, e duo septimanas plus tarde le schema congrueva con acute leucemia monoblastic. Marcate grados de erythrophagocytose per blastocytos in le medulla esseva notate. Le patiente moriva post sever hematemese e melena.

Le necropsia revelava infiltration de splen, medulla ossee, hepate, renes, e adrenales per atypic cellulas primitive que habeva nucleos vesicular e un abundantia de cytoplasma basophilic.

Le differentiation inter myelosis erythremic e varie formas de anemia perniciose es discutite. In le presente caso, omne investigationes visante a demonstrar o excluder le formas plus usual de anemia hemolytic esseva negative. Un marcate reduction del longevitate erythrocytic esseva demonstrate. Estimationes del super-viventia erythrocytic non es necessarimente de adjuta in differentiar myelosis erythremic ab bizarre formas de anemia hemolytic. Le constatation de un normal nivello seral de vitamina B_{12} indica que iste investigation es possibilemente de valor in distinguer anemia perniciose ab myelosis erythremic.

Le reaction de Hotchkiss pote esser de valor diagnostic in myelosis erythremic, sed illo non pote distinguer ille condition ab thalassemia major.

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CARDIAC INVOLVEMENT IN REITER'S DISEASE: REPORT OF A CASE WITH REVIEW OF THE LITERATURE *

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Reiter's disease is a syndrome of unknown etiology, characterized by arthritis, urethritis and conjunctivitis. The clinical components of this syndrome are still in dispute. For example, many investigators will not accept the diagnosis unless the classic triad is present.[1, 2] Paronen,[3] in his series of 344 cases, found the triad present in 69.8%; Hollander [4] noted it in only 11 of 25 cases. The etiology as well as the effective therapy of this disease is still in doubt. Many authors [1, 2, 5, 6, 7] have described in detail the ubiquitous character of Reiter's disease but have given little attention to the incidence of cardiac involvement. The purpose of this paper is to report a case of Reiter's disease with myocarditis, and to present a review of the type and incidence of cardiac involvement in this syndrome.

Case Report

A 23 year old white male entered the St. Louis Veterans Administration Hospital for the first time on January 28, 1958. The present illness had begun in October, 1955, when he developed a purulent urethral discharge and was treated with sulfa drugs. A recurrent episode occurred several months later, which was treated in similar fashion. He denied any sexual contact, and stated that on each occasion he had been assured by the physician treating him that he had no "venereal disease." On December 13, 1957, the urethritis recurred for the third time, followed in several days by pain and swelling in the right knee, with later involvement of the right hip. There was an associated low grade temperature, up to 100.2° F. The right knee was aspirated on four separate occasions by a local physician, and "clear yellow fluid" was obtained each time. The patient denied conjunctivitis, antecedent sore throat, diarrhea, or trauma to the involved knee. Past history, family history and systemic review failed to elicit contributing factors.

The examination revealed a well developed, well nourished white male in no acute distress. Vital signs were recorded as follows: blood pressure, 90/76 mm. of Hg; pulse, 82; temperature, 98.6° F. Examination of the ears, eyes, nose and throat demonstrated them to be within normal limits. The lungs were clear to percussion and auscultation. Examination of the heart revealed no cardiomegaly, thrills or murmurs. The abdomen contained no palpable organs, and no guard or tenderness

* Received for publication January 27, 1959.
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was present. The genitalia were within normal limits. Examination of the lower extremities revealed a diffusely swollen, tender right knee, with no limitation of motion. The right patella was ballotable, indicating the presence of joint fluid. The findings on neurological examination were within normal limits. Rectal examination revealed no palpable masses, hemorrhoids or prostatic tenderness. A small area of subungual keratosis of the left middle finger was noted.

X-ray chest film was negative. Cardiac fluoroscopy was unrevealing. An x-ray of the right knee on repeated occasions failed to demonstrate bone or joint abnormalities.

Admission urinalysis revealed a specific gravity of 1.015 and a trace of albumin, with an occasional white blood cell on microscopic examination. The hemoglobin

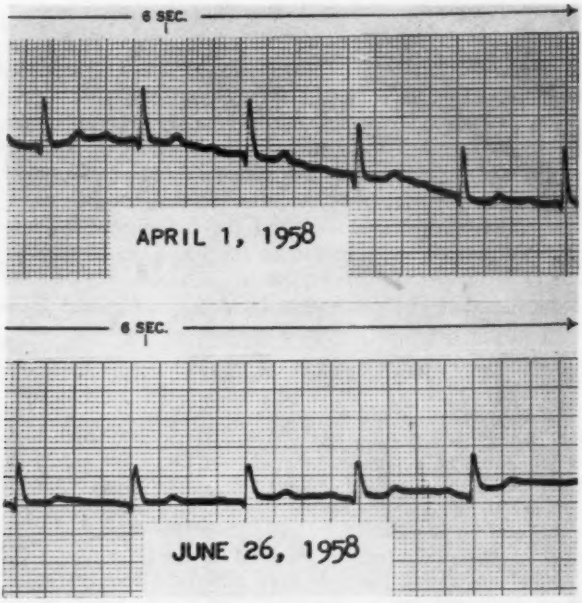


FIG. 1. Representative electrocardiograms, Lead 3, which reveal P-R intervals of 0.28 second and 0.18 second, respectively.

was 14.9 gm. per 100 c.c.; hematocrit, 44; white blood cell count, 6,400, with a normal differential. Initially the sedimentation rate was 21 mm. per hour, but it subsequently returned to normal. Repeated cultures of the yellow transparent fluid aspirated from the right knee were sterile for bacteria, fungi and acid-fast bacilli. The result of the serologic test for syphilis as performed with the Venereal Disease Research Laboratory (VDRL) antigen was negative. The anti-streptolysin O (ASO) titer on several determinations did not rise above 100 Todd units. Uric acid levels were within normal limits. Latex fixation and sheep cell agglutination studies for rheumatoid arthritis were negative. Serum proteins were within normal limits. Serial electrocardiograms revealed a first degree A-V block, with P-R intervals ranging from 0.32 second to 0.22 second (figure 1). At time of hospital discharge the P-R interval was 0.19 second. The first strength PPD was negative,

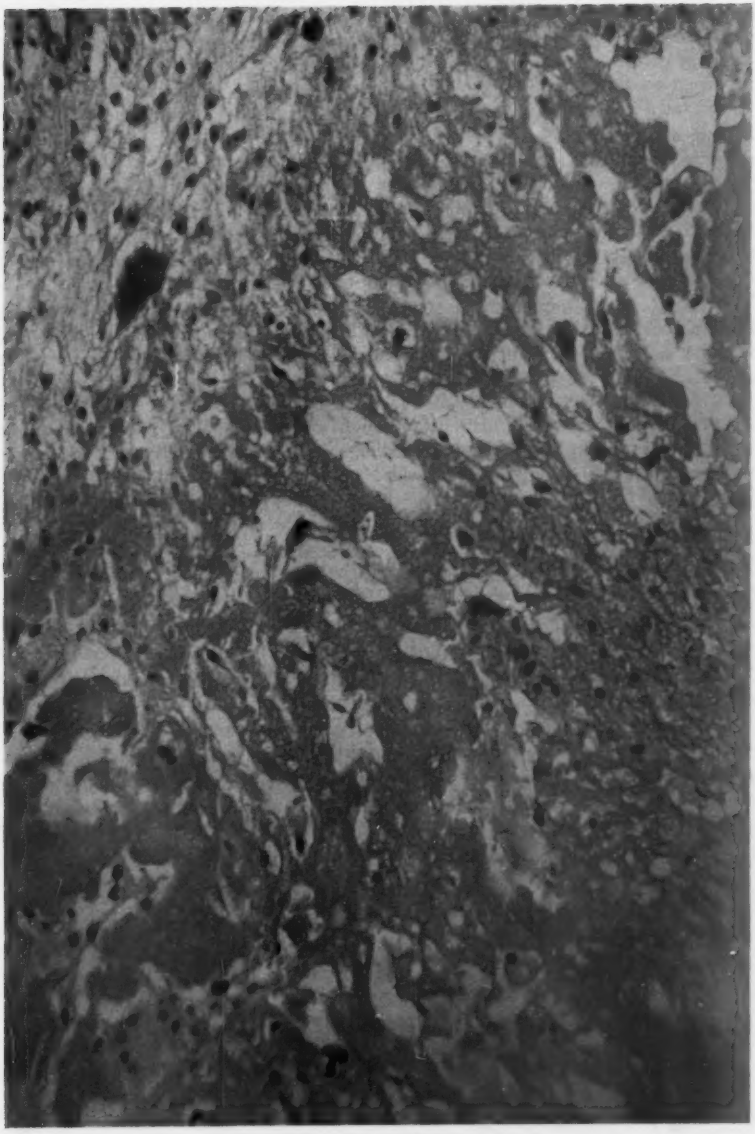


FIG. 2. A photomicrograph of the biopsy specimen taken from the involved right knee. There are localized areas of necrosis with profuse fibrin formation. A paucity of inflammatory cells and one giant cell are also to be noted.

the second strength was positive in 48 hours. A biopsy of the right knee joint performed in June, 1958, revealed a nonspecific fibrinous synovitis (figure 2).

Repeated aspirations of the right knee revealed a sterile clear yellow fluid. A trial of colchicine (0.5 mg. per hour) was made until diarrhea ensued, but with no improvement of the involved knee. Salicylate therapy in dosages up to 120 gr. per day produced partial amelioration of the joint symptoms. Meticorten administered orally, and intra-articular injections of hydrocortisone were without benefit.

During the period of delayed A-V conduction in the electrocardiograms, no drugs were being administered which are known to produce such a conduction defect. On several occasions, heart sounds suggestive of a diastolic rumble were heard at the apex. Subsequent phonocardiography revealed this to be either a normal third heart tone or a diastolic gallop. The patient was discharged March 26, 1958, on 60 gr. of salicylates per day, only to return on several subsequent occasions with recrudescence of the aforementioned joint symptoms.

The diagnosis of Reiter's disease was made on the basis of recurrent aseptic urethritis associated with a sterile, nonmigratory arthritis. The lack of response to colchicine and the normal uric acid levels ruled out gout. The absence of a rise in the ASO titer during the active period, coupled with the nonmigratory character of the arthritis and the chronicity of the disease, made rheumatic fever unlikely. The diagnosis of rheumatoid arthritis, though considered, was not substantiated by latex or sheep cell agglutination studies. The absence of roentgenographic findings or response to steroid hormone therapy was also inconsistent with this diagnosis.

Discussion

Scant information is available regarding the incidence of cardiac involvement in Reiter's disease. Paronen's series of 308 cases contained 20 with electrocardiographic abnormalities. An additional three patients presented with a pericardial friction rub, making a total of 23 cases with cardiac involvement. Of these 23, four had myocarditis and pericarditis, three pericarditis alone, and 16 myocarditis only. The aforementioned diagnosis of myocarditis was made by electrocardiograms, whereas the pericarditis manifested itself by both auscultatory findings and electrocardiographic changes. Mavioglu,[2] in a review of 132 cases, found the incidence of myocarditis to be 1.4%. Additional reports of cardiac involvement in Reiter's disease, excluding the two abovementioned series, total 20.[2, 4, 5, 7, 9, 11-13, 15-17] The electrocardiographic abnormalities are summarized in table 1. S-T segment displacement, P-R prolongation and T wave changes

Table 1

Electrocardiographic Abnormality	Number of Patients
Abnormal Q waves	2
S-T segment displaced (usually elevated)	7
P-R prolongation	14
Low voltage	1
T wave abnormalities	8
Occasional VPC	1
Trigemini	1

are the most predominant irregularities. Three cases in this group suggested pericarditis with S-T segment elevations, while seven displayed auscultatory irregularities. The latter are summarized in table 2. It is noted that transient apical systolic murmurs and pericardial friction rubs predominate.

In general, patients with Reiter's disease manifesting myocarditis as demonstrated by electrocardiographic abnormalities are free of cardiac symptomatology. The same was true in our case. The incidence of cardiac involvement as reflected in our review is approximately 12% (45 of 364). Since the majority

TABLE 2

Auscultatory Abnormality	Number of Patients
Apical systolic murmur	4
Pericardial friction rub	2
Mesodiastolic gallop	1
VPC	1
Trigemini	1

of these patients had an asymptomatic myocarditis, the routine use of electrocardiography is urged to alert the clinician to the presence of an unsuspected cardiac involvement. Such an approach may also aid in properly defining the cardiac manifestations in this syndrome.

CONCLUSION

A case of Reiter's disease with myocarditis manifested by first degree A-V block is presented. The incidence and type of cardiac involvement noted in this syndrome complex are reviewed. Usually this presents no clinical symptomatology. Thus routine use of electrocardiography is recommended.

SUMMARIO IN INTERLINGUA

Es presentate un caso de morbo de Reiter con evidentia de myocarditis. Ben que le symptomatologia contineva nulle elemento que poteva esser ascribite al corde, le electrocardiogramma al tempore del admission al hospital revelava le presentia de un bloco cardiac del prime grado. Iste anormalitate persisteva durante le plus grande parte del duo menses del sejorno hospitalari del patiente e reverteva al norma brevemente ante su dimittimento.

Le ver incidentia de iste complication non es cognoscite. In le reportate casos de syndrome de Reiter in que le stato cardiac habeva specificamente essite examinate, 12% manifestava anormalitates auscultatori o electrocardiographic. Le anormalitates auscultatori consisteva de transiente murmures systolic apical, de ruitos de friction precordial, o de rhythmo de galopo. Le anormalitates electrocardiographic includeva disturbationes de rhythmo o de conduction, displaciamento del segmento S-T, o alteration del unda Q o del unda T.

Como il esseva ver in le caso hic reportate, le majoritate del patientes con morbo de Reiter in association con myocarditis ha nulle symptomas que suggere le presentia de un affection myocardial. Per consequente, il es recommendate urgentemente que un precise auscultation cardiac es effectuate e que electrocardiogrammas es obtenite in omne casos de morbo de Reiter, de maniera que le ver incidentia del manifestation cardiac pote esser determinate.

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GIANT FOLLICULAR LYMPHOBLASTOMA TERMINATING IN ACUTE MYELOGENOUS LEUKEMIA*

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A number of instances of malignant lymphoma terminating in leukemia have been reported. In most of these cases the ultimate leukemic cell type has usually been one of a variety of the lymphocytic series.[1,2,3,4] However, a report published in 1954 concerned a patient with reticulum cell lymphoma whose final event was acute myeloid leukemia.[5] We wish to add another instance of this unusual association by reporting a case of giant follicular lymphoma that terminated in acute myelocytic leukemia.

CASE REPORT

The patient was a 43 year old housewife whose first symptoms developed in April, 1950, when she noted sharp, shooting pains in the region of the umbilicus, not affected by eating or exercise. Her appetite was good and the bowels were regular. When she was examined in May, 1950, an indefinite resistance was thought to be present in the umbilical area. A gastrointestinal x-ray series with special small-bowel studies was normal, and a barium enema was normal. In June, 1950, the pain became less intense, and a complete blood count showed normal values, with a sedimentation rate of 7 mm. per hour. The patient was not seen again until December, 1950, when she complained of vague pain across the lower chest and in the upper abdomen, which gradually subsided. In April, 1951, there was a recurrence of indigestion, with nausea and occasional vomiting, and examination revealed a more definite mass in the periumbilical area.

Finally, in November, 1951, the patient entered the Washington County Hospital, where an exploratory operation revealed the presence of many enlarged mesenteric lymph nodes, ranging from ½ to 1 inch in diameter. One of the largest nodes was removed for study. The liver, stomach, spleen and kidneys were grossly normal. A hysterectomy was done because of myomata, and the appendix was routinely taken out. Sections of the removed gland showed follicular lymphoblastoma (figure 1). A blood count at this time was as follows: erythrocytes, 3.74 million; hemoglobin, 71.4%; leukocytes, 8,000, with polymorphonuclears, 49%, stab forms, 5%, lymphocytes, 44%, and monocytes, 2%. Following the patient's discharge after an uneventful recovery, x-ray therapy was started on December 3, 1951. These treatments were administered in rapid succession (every day or every other day, as the patient's condition permitted) up to and including February 21, 1952. Standard opposing paravertebral portals were used, covering the spine from the mediastinum to the pelvis. The portals measured approximately 15 by 8 cm. A total of 2,500 roentgen units (in air) was administered through each portal. Following these treatments, the abdominal mass could no longer be felt.

The patient then felt well, and periodic examinations revealed no change until early 1954, when an enlarged gland was noted in the right axilla. This was excised March 1, 1954, and the pathologic report was giant follicular lymphoma (figure 2). A blood count at this time was as follows: erythrocytes, 3.59 million; hemoglobin,

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10.5 gm.; leukocytes, 5,000, with polymorphonuclears, 65%, stab forms, 7%, lymphocytes, 26%, monocytes, 1%, and basophils, 1%. Several small, shotty glands developed in the neck and groins in March, and in April, 1954, the patient received 1,000 r (in air) in four treatments to the right axilla.

In early 1955 the patient noticed fatigue and headaches. A cyst was removed from the area over the third incisor on the right upper jaw, following which the headaches improved. A blood count on May 18, 1955, revealed the following: erythrocytes, 2.78 million; hemoglobin, 9.0 gm.; hematocrit, 26%; leukocytes, 4,100, with polymorphonuclears, 55%, lymphocytes, 43%, eosinophils, 1%, and basophils, 1%; platelets, 90,090. On May 20, 1955, a sternal bone marrow smear showed: granulocytic cells, 80.5%; nongranulocytic cells, 7.5%; erythroid cells, 12%. The



FIG. 1. Section of mesenteric gland, removed November 14, 1951, showing the usual pattern of follicular lymphoblastoma. (Hematoxylin and eosin, × 25.)

slightly increased number of granulocytic cells was due largely to some increase in the myelocytes, metamyelocytes and segmented granulocytes; however, the marrow in general was not diagnostic of a granulocytic leukemia. On May 23, 1955, the patient was given two pints of blood. On June 3, 1955, she was referred to the Memorial Hospital in New York City for consultation. Her blood study was reported as follows: erythrocytes, 4.20 million; hemoglobin, 12 gm.; leukocytes, 4,900, with filaments, 45%, nonfilaments, 11%, mature lymphocytes, 31%, atypical lymphocytes, 1%, monocytes, 2%, eosinophils, 1% paramyeloblasts, 4%, myelocytes, 4%, and unclassified monocytes, 1%; platelets, 88,200. Slides of the mesenteric and axillary nodes sent with the patient were reviewed and interpreted as follicular lymphosarcoma. The over-all clinical impression was that of a giant follicular lymphoma, gradually metamorphosing into a true lymphosarcoma. At this time, enlarged nodes were present in both sides of the neck, axillae and groins, and further x-ray

therapy was recommended. Accordingly, within the next two weeks the patient received a total of 3,000 r (in air) to the right and left axillae, right and left cervical node chains, and the right and left inguinal lymph nodes. Several additional blood counts, taken between the completion of her x-ray therapy and her final hospital admission, showed comparatively little change in the degree of anemia, but a decreasing number of platelets (from 46,400 on June 16, 1955, down to 14,000 on July 12, 1955). In the week prior to admission she developed a number of hemorrhages into the skin, and noted a feeling of tightness and wheezing in the upper part of the chest. The day of admission she noted blood in her stools. She had been receiving an average of two transfusions a week since late May, but in spite of this had felt ill and had been running fever.

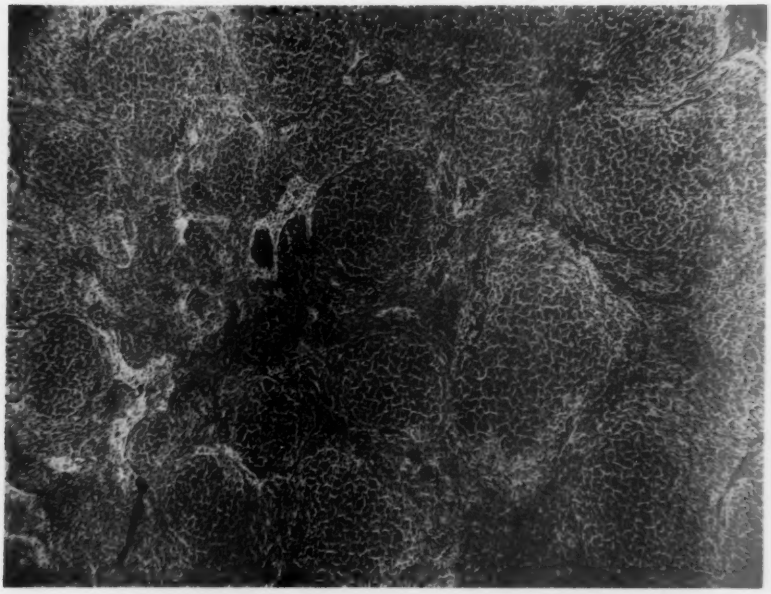


FIG. 2. Section of axillary lymph node, removed March 1, 1954. (Hematoxylin and eosin, × 25.)

Because of her unfavorable course the patient reëntered the Washington County Hospital on July 13, 1955. Physical examination revealed a sallow, middle aged white female who appeared to be chronically ill. The skin showed ecchymotic areas of varying size, as well as a few small petechial spots. Most of these were located on the arms, over the chest wall and on the legs. The mucous membranes were pale. The pupils and ocular motions were normal. The fundi were normal except for one small splinter hemorrhage adjacent to a retinal artery in the left fundus. The patient had had some bleeding from the gums, and there was one ecchymotic area just above the third left upper incisor. Several small petechiae were scattered through the mouth. The neck showed no rigidity, and the thyroid gland was not palpable. No definite nodes were felt in the neck or axillae. The heart was not remarkable, and the blood pressure was 82/60 mm. Hg. The lungs were clear except anteriorly on both sides over the upper portions, where wheezing breath sounds were

noted. The abdomen was soft and not tender; the liver and spleen were not palpable; an old, low midline scar was present. The lower part of the abdomen in the center revealed some doughy resistance but no definite mass. No inguinal glands were palpable. The extremities were negative except for the ecchymotic areas mentioned above. No ankle edema was present on admission. There were no abnormal neurologic findings.

Course in Hospital: There was fever of varying degree throughout hospitalization. One week after admission a bout of gross hematuria occurred, and later that same day the patient had five rectal hemorrhages, losing an estimated 1½ pints of blood. A sternal bone marrow biopsy (figure 3) on July 25, 1955, showed the marrow to be slightly hyperplastic, and megakaryocytes to be practically absent.

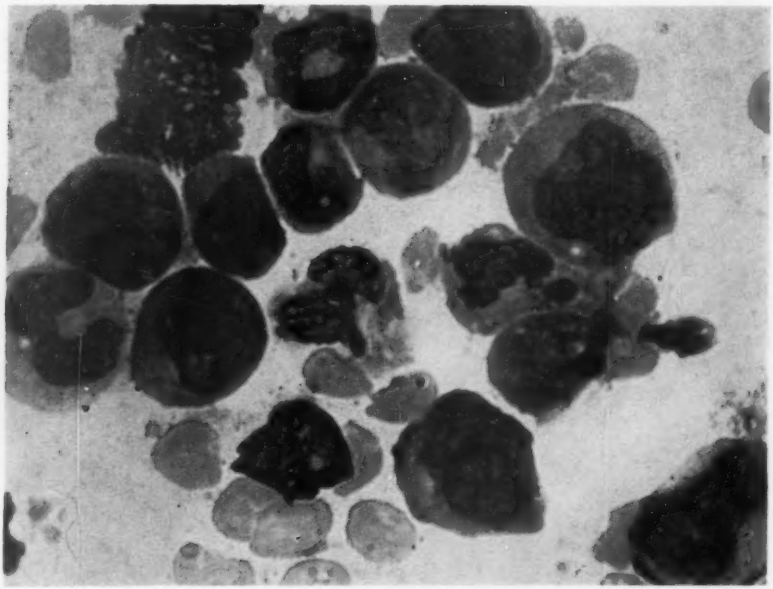


FIG. 3. Representative field of sternal bone marrow smear, July 25, 1955, showing predominance of immature granulocytes. (× 1000.)

The count was as follows: myeloblasts, 16%; promyelocytes, 14%; myelocytes, 6.7%; metamyelocytes, 42.7%; segmented polymorphonuclears, 9.0%; lymphocytic and monocytic series, 7.3%; erythroid series, 3.6%. The impression from study of this marrow was acute myeloid leukemia. The hemoglobin ranged from 9.3 gm. down to 2.8 gm., while the erythrocyte count ranged from 3.5 million to as low as 1.12. An indirect Coombs' test was negative. Reticulocytes ranged from 0 to 0.3%. Bleeding and clotting times were within normal limits. Serum bilirubin was 0.4 mg. A number of leukocyte counts showed a range of 3,900 to 12,300; however, most were from 5,000 to 6,000. The admission differential count showed: polymorphonuclears, 81%; lymphocytes, 16%; monocytes, 1%; the count contained the comment: "Many unidentified young forms" (figure 4). A number of other differential counts during hospitalization were of about the same order. Platelet counts in the first 10 days showed a range of 10,000 to 15,000; thereafter they decreased, and the last five

counts revealed no platelets at all. Therapy consisted of cortisone, 6-mercaptopurine, 16 pints of blood and various symptomatic measures. The outstanding feature of the patient's gradual downhill course was the marked bleeding tendency, characterized by the recurrent petechiae, ecchymoses, hematuria and the rectal bleeding. She died on August 21, 1955.

Autopsy (Condensed): The body was that of a middle aged white female. Scattered and numerous purpuric spots were seen over the trunk, abdomen and extremities. Pitting edema of the lower extremities was present. There was no icterus or significant superficial lymphadenopathy.

Each pleural cavity contained about 400 c.c. of yellowish fluid. The mediastinal lymph nodes varied from 1 to 2 cm. in diameter. The lungs were pale and showed

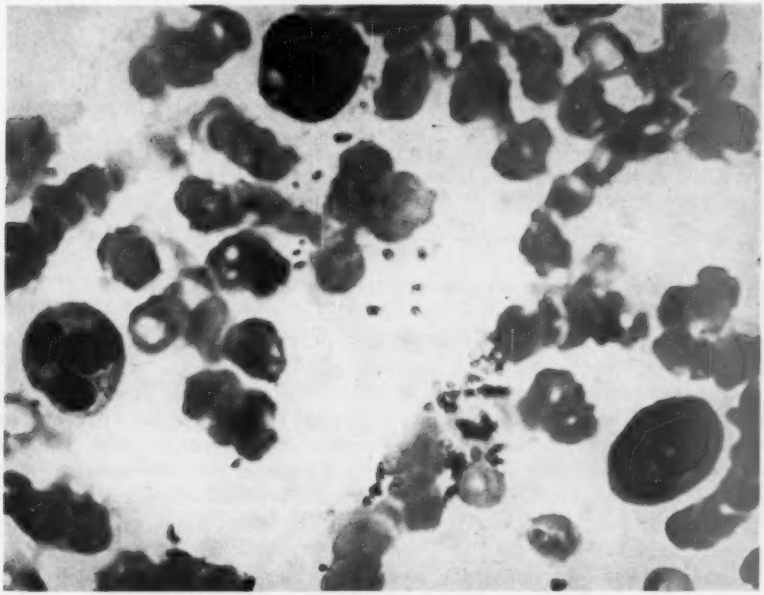


FIG. 4. Peripheral blood, July 14, 1955, showing immature granulocytes. (Wright stain, × 1000.)

petechial hemorrhages and areas of lobular atelectasis. The alveolar walls were thin, and the alveolae contained a few large, pigment-laden macrophages. The right lung weighed 400 gm., and the left, 450 gm.

The heart weighed 350 gm. There was no significant abnormality beyond subepicardial and subendocardial petechial hemorrhages.

The peritoneal cavity contained about 700 c.c. of yellowish fluid. The liver descended 3 cm. below the costal margin and weighed 1,350 gm. On cutting there was slight increase in resistance, and some accentuation of the lobular pattern was noted. Microscopically the liver presented no change beyond passive congestion.

The spleen was essentially normal in size, weighing 100 gm.; the parenchyma was soft and of a pale reddish purple. The capsule and trabeculae of the spleen were infiltrated with a few lymphocytes. Malpighian corpuscles were of average size and poorly defined. The red pulp contained relatively few red cells, but

numerous mature lymphocytes and scattered, pigment-laden macrophages. Cellular anaplasia and mitotic figures were not seen.

The mucosal surface of the stomach appeared to be markedly hemorrhagic, and the serosal surface showed a few petechial hemorrhages. The duodenum was not remarkable. The pancreas was normal except for a few small foci of interlobar fibrosis on section. The serosa of the small and large intestine showed numerous petechial hemorrhages, and these were also noted on the mucosal surface of the sigmoid colon and rectum. A globular mass of clotted blood was found in the cecum.

Except for pallor, the kidneys were not remarkable, and sections of the adrenals and kidneys showed nothing unusual.

The hilar lymph nodes showed, in general, a well preserved architecture, with moderate anthracotic pigmentation. The sinusoids were distended with macrophages, red cells and lymphocytes. Sections of the lymph glands in other situations showed distortion of the architecture by fibrosis and fatty metamorphosis. Lymphoid elements, which showed no anaplasia, did not appear to form distinct follicles, but rather were seen as anastomosing cords and nests of cells with, at times, dense infiltration of these cells into and beyond the capsule. The connective tissue infiltration appeared to be distinctly neoplastic.

The final anatomic diagnosis was: giant follicular lymphoblastoma; purpura, generalized (acute myelogenous leukemia?); lobular atelectasis of the lungs; hemorrhage, gastrointestinal; pallor of the viscera; peripheral edema; ascites.

Discussion

While giant follicular lymphoma pursues a slow, "benign" clinical course, Diamond [6] has pointed out that sooner or later a transition occurs to a more malignant type, such as follicular lymphosarcoma, reticulum cell sarcoma, "diffuse" lymphosarcoma or even leukemia, all of these being in the same general cell-type category. The development of leukemia in these cases is in itself rather unusual, but the transition into a myeloid type of leukemia is even rarer. The occurrence of acute myelocytic leukemia in this patient with malignant lymphoma is conceivably on the basis of a change in the differentiation of the stem cell from the lymphoid to the granulocytic type, as suggested by Beutler.[5] However, the possibility that the two conditions were associated by reason of exposure to radiation seems worth consideration, although it is speculative.

Leukemia has been one of the neoplasms most frequently induced by radiation, both in man and in experimental animals. In follow-up studies of atomic bomb survivors in Nagasaki and Hiroshima, Folley et al.[7] found an increased incidence of leukemia with respect to the distance of the survivor from the site of the blast. Myelocytic leukemia was found to be the predominant type, with only one instance of chronic lymphatic leukemia. Myelocytic leukemia has also been reported following the treatment of thyroid carcinoma with radioiodine.[8]

Conclusion

A case has been reported of giant follicular lymphoma terminating in acute myelocytic leukemia. The possibility that the development of the latter condition was influenced by radiation therapy merits consideration.

Acknowledgments

The author wishes to acknowledge the helpful coöperation of Dr. James H. Ramsey for the hematologic studies, and of Dr. Roy B. Turner for the pathologic studies.

SUMMARIO IN INTERLINGUA

Un numero de casos de lymphoma maligne con termination in leucemia se trova reportate in le litteratura. Le leucemia in question esseva usualmente un variante ex le serie lymphocytic. Le presente reporto concerne le caso de un patiente con lymphoma giganto-follicular que se terminava in acute leucemia *myelocytic*. Le patiente esseva un femina de 43 annos de etate. Su maladia comenciava con symptomas gastro-intestinal e un massa abdominal. Illo sequeva un lente e intermittente curso durante un anno e medie. Post iste antecedente, le patiente se subjiceva finalmente a laparotomia exploratori. Esseva trovate multe grande nodos lymphatic mesenteric. Un de istos manifestava lymphoblastoma follicular in le studio pathologic. Post roentgeno-therapia, le massa abdominal dispareva, e le patiente se portava comparativemente ben durante le sequente duo annos e medie. Alora illa recipeva de novo un curso roentgenotherapeutic pro adenopathia axillar, proque le biopsia de un glandula habeva monstrate de novo le presentia de lymphoma giganto-follicular. Approximativemente un anno post iste secunde curso, le patiente disveloppava anemia e phenomenos hemorrhagic. Le studio del medulla ossee indicava acute leucemia myelocytic. Le subsequente curso clinic reflecteva un rapide deterioration, e le morte superveniva approximativemente cinque annos e medie post le declaration del prime symptomas. Pertinente datos necroptic es includite in iste reporto.

Per contrasto con lo que occurre in leucemia lymphocytic, le disveloppamento de leucemia myelocytic como evenimento terminal in lymphoma es multo inusual. Le possibilitate de un transition del differentiation del cellula primordial ab le typo lymphoide ad le typo granulocytic ha previemente essite proponite pro explicar iste phenomeno. Del altere latere, leucemia myelocytic es le typo le plus frequente de leucemia reportate post exposition a effectos irradiatori. In le presente caso individual, le influentia del roentgeno-therapia merita esser prendite in consideration como factor in le disveloppamento del leucemia.

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EDITORIAL

IMMUNITY TO TISSUE GRAFTS

It has long been common knowledge that if skin is grafted on human subjects, only autografts, from the same individual, survive. Homografts, from other individuals of the same species, are rejected except when the donor and recipient are identical twins with exactly the same antigens. This has been found true of all vertebrates studied, from fish to monkeys.

If some means could be found to circumvent this process of rejection of the graft, it would be a therapeutic triumph of major importance. It should make possible not merely homografts of skin but of tissues generally, including the transplantation of intact organs and the introduction of hematopoietic cells in the treatment of presently fatal radiation sickness and of acute leukemia. This problem has attracted many investigators, and a large literature has accumulated. Skin grafts have been most extensively studied, but this is largely because of their convenience. Other tissues behave similarly.

In the case of an organ or large piece of tissue, the circulation must be surgically reëstablished promptly to secure survival. In the case of autografts of skin or thin slices of organs, if embedded in well vascularized tissue this is ordinarily not necessary, as the small vessels of the tissue and graft quickly become connected, circulation is reëstablished, and the grafted tissue remains functional and healthy. This is also true of most homografts at first, but soon the homograft becomes inflamed, it is infiltrated with lymphoid cells and phagocytes, the vessels become thrombosed, the graft separates and breaks up into a necrotic slough. This is quite independent of infection or errors of surgical technic.

As pointed out by Medawar,[1] this incompatibility is not initially present, but it develops as the result of a specific immunologic reaction. The duration of survival of the graft is a measure of the intensity of the reaction. If a second graft from the same donor is applied after the first graft has been shed, it is rejected more promptly, often within two or three days. This accelerated reaction is an indication of acquired resistance ("immunity") on the part of the host. This resistance is specific as to the individual but not as to tissue. Any tissue grafted will make the recipient immune to all tissues of the donor. If, however, a second homograft is made from a different donor, this will usually survive as long as the initial graft.

This immunity does not depend upon any demonstrable antibodies in the serum, and it can not be passively transferred by serum. If, however, regional lymph nodes from a mouse which has rejected a graft are inoculated

[1] Medawar, P. B.: The immunology of transplantation, Harvey Lectures, Ser. 52, 1957, p. 144.

or implanted in a normal mouse of the same strain, this mouse will show an accelerated reaction to a graft from the same donor.[2] The immunity depends upon substances ("antibodies") fixed firmly to these cells. It is believed that antigens from the graft reach neighboring lymph nodes and stimulate the lymphoid cells to proliferate and produce the (fixed) antibodies. These cells then pass by the blood or lymph back into the graft which is destroyed by them, although the exact mechanism of this process has not been demonstrated. Berrian et al.,[3] utilizing ingenious experiments with a diffusion chamber, have reported that homografts will survive if intact (lymphoid) cells are prevented from entering the graft. The cells must be alive in order to exert either antigenic or protective activity. Cell-free homogenates or cells which have been disrupted by ultrasonic vibration, e.g., are inert.

To determine the mechanism of these reactions more precisely and if possible devise some means of forcing a subject to "accept" or "tolerate" a homograft, a study of inbred ("isogenic") strains, particularly of white mice, has been helpful.[4] These strains are produced by brother-sister matings over many generations so that all members of the strain become identical antigenically and will accept an "isograft" from any other mouse of the same strain but not from those of different inbred strains. It has been shown that these differences in antigenic strain in mice are determined by certain specific genes, "histocompatibility genes," and that there are at least 15 different loci in the chromosomal apparatus in which one or more of these genes may be found. These differ considerably in the degree of antigenic difference and consequently in the severity of the reaction which they determine in an incompatible host. A graft will be accepted if all its significant antigens are present in the tissues of the host. If some antigens in the graft are not present in the host, the "immunologically competent" cells of the host, the lymphoid cells and plasma cells, will "recognize" them as foreign, an immunologic defense reaction will be stimulated, and the graft will be rejected.

This can be illustrated by the behavior of the F_1 hybrids, produced by mating two mice from different isogenic strains. Such hybrids receive a complete set of chromosomes from each parent. If tissue from either parent is grafted on such a hybrid, the latter finds no strange antigens in the graft and "tolerates" it. If tissue from the hybrid is grafted onto either parent, however, the tissues of the latter (the host) will meet with antigens foreign to it in the graft (derived from the other parent of the hybrid), a defense reaction in the host is stimulated, and the graft is rejected. An F_1 hybrid as a recipient, therefore, affords one situation in which a homograft will be

[2] Mitchison, N. A.: Passive transfer of transplantation immunity, Proc. Roy. Soc., London s. B. **142**: 72, 1954.

[3] Berrian, J. H., and Brent, L.: Cell bound antibodies in transplantation experiments, Ann. New York Acad. Sc. **73**: 654–661, 1958.

[4] Billingham, R. E.: Reactions of grafts against their hosts, Science **130**: 947–953, 1959.

accepted, a special situation very useful for investigative purposes but unpromising as a direct lead to any practicable therapeutic procedure.

Much has been learned from a study of fetal and new born animals. It has long been known that the very young are unable to form antibodies to microörganisms. Foreign cells or tissues can be inoculated into chick embryos and survive and grow there, although causing splenomegaly in the embryo. Living cells, such as adult myelogenous or splenic cells injected into infant mice or chickens, survive and in fact show a strong "homing" tendency, "an uncanny capacity" [4] to settle out in the corresponding organs of the host and proliferate there, seemingly a remarkable feat for the supposedly nonmotile lymphoid cells. The host frequently if not usually responds by becoming "tolerant" of them; their antigens are subsequently interpreted as familiar by the host, and no reaction to them is incited. The host becomes a chimera, harboring and living in symbiosis with tissues from another individual. If such a chimera survives, it is believed that the donor's cells survive in it for at least a year if not indefinitely.[5]

Such tolerance can be created only in the very young, in some species only in fetal life, but if established it may persist for long periods, even for much of the life span of the host. It covers all tissues, transplants and inoculated cells survive, but tolerance is strictly limited to the individual donor or one of the same isogenic strain. Such tolerance is not absolute nor necessarily of indefinite duration. It is really effective and dependable only when the antigenic differences are moderate.[6]

The mechanism of this tolerance is not known. It recalls in some respects the "immunological paralysis" described by Felton.[7] If a huge dose of pneumococcal polysaccharide was injected into a mouse, the animal gave no response when a subsequent attempt was made to immunize it to this material by the usual schedule of doses effective in untreated mice. The polysaccharide was stored in large quantities in the tissues of the mouse, since extracts of its tissues in suitable doses would immunize normal mice to this strain of pneumococcus. It is still not certain whether this is literally a paralysis of this particular immunologic process or whether antibodies are actually produced but immediately neutralized by the excess of antigen of which the mouse has not been able to dispose.

Hildemann [6] believes that tolerance to transplanted homologous tissues depends upon the persistence of the donor's cells in the recipient. If normal lymph nodes from a mouse of the same isologous strain are implanted in such a tolerant mouse, it may lose its tolerance. The implanted lymphoid

[5] Barnes, D. W. H., Ford, C. E., Ilbery, P. L. T., and Loutit, J. F.: Tolerance in the radiation chimaera, Transplantation Bull. **5**: 101–106, incorporated in Plast. and Reconstruct. Surg. **22**, 1958.

[6] Hildemann, W. H.: Specific modifications of the immune response, Transplantation Bull. **5**: 97–101, incorporated in Plast. and Reconstruct. Surg. **22**, 1958.

[7] Felton, L. D., Kauffman, G., Prescott, B., and Ottinger, B.: Studies on mechanism of immunologic paralysis induced in mice by pneumococcal polysaccharides, J. Immunol. **74**: 17–26 and 205–213, 1955.

cells correctly recognize the initially inoculated foreign cells as strange and react against them, even though the host's own cells presumably take no active role in the reaction.

It has also been suggested that some immunologic alteration or adaptation of the graft to the host occurs in those mice in which tolerance is developed in infancy.[8] Thus, it has been observed that a chick which had been made tolerant by an early injection and which carried a successful homograft nearly always rejected a second homograft from the same donor. If one of a pair of cross-transfused chicks was given a graft from the other on the second day, and again a similar graft on the fifteenth day, both were rejected, but the latter graft was sloughed first. On the other hand in rats made tolerant by intrauterine injection, a graft that had survived three months could be replaced successfully on the original donor.[9] In chicks Cannon[10] observed that under similar circumstances grafts retained to the adult stage could be so returned successfully in 50% of the cases. There could, therefore, have been no profound antigenic changes in these grafts.

Undoubtedly there are progressive changes both in antigenic structure[8, 11] and in the capacity to form antibodies as these infantile animals mature. In some species these characters are fairly advanced at birth, whereas in others a similar stage is not reached until several days later. In the earliest developmental stages some alteration or adaptation has apparently been secured. The changes that occur with progressive maturation tend to increase and fix the antigenic differences, and in the animals carefully studied after the age of a week or two and usually less, little if any significant or possibly useful alteration in their immunologic mechanism has been achieved.

Efforts have been made to utilize the adaptive property of very young tissues by grafting human fetal skin on open lesions of adult subjects. Baxter et al.[12] obtained good initial survival in all cases using grafts from 19 fetuses 16 weeks or more in age, but none survived more than 46 days. Using grafts from younger fetuses in six cases, he obtained survival for seven to 13 weeks. Snyderman[13] also reported survival in four of eight cases.

Extensive studies on newly hatched chicks have also been made. Cannon et al.[10] found, as have others, that crossed homografts in chicks on the

[8] Cannon, J. A., Terasaki, P., and Longmire, W. P., Jr.: Unexpected manifestations of induced tolerance in skin homografts in chicks, Ann. New York Acad. Sc. **73**: 862–868, 1958.

[9] Egdahl, R. H., Roller, F. R., Swanson, R. L., and Varco, R. S.: Acquired tolerance to homografts and heterografts in the rat, Ann. New York Acad. Sc. **73**: 842–847, 1958.

[10] Cannon, J. A., Terasaki, P., and Longmire, W. P.: Study of factors influencing induced tolerance to skin homografts in the chicken, Ann. Surg. **146**: 278–284, 1957.

[11] Egdahl, R. H.: Immunological maturation and defects in immunological capacity, Transplantation Bull. **5**: 87–97, incorporated in Plast. and Reconstruct. Surg. **22**, 1958.

[12] Baxter, H., Goldstein, M. A., and McMillan, G. C.: The fate of human fetal homo- and heterografts, Transplantation Bull. **5**: 516–524, incorporated in Plast. and Reconstruct. Surg. **22**, 1958.

[13] Snyderman, R. K.: Clinical application of embryonic skin grafts, Ann. New York Acad. Sc. **73**: 561–563, 1958.

second day were retained in about 5 to 10%, but a second graft from the same donor later was nearly always rejected. Grafts applied to chicks over seven days old or grafts from chicks over 13 days old, even if applied to hatchlings, were likewise rejected.

Attempts to improve these results were made by inducing tolerance. A method was devised for cross-transfusing embryo chicks.[10] When these were cross grafted on the second day after hatching, the grafts were successful in 81%, as compared with 9.2% in the controls; and when done on the fifteenth day they were successful in 52%, as compared with only 2.8% in the controls. Such grafts were still surviving six months later in 40% of those which had been so transfused. Increased but not permanent tolerance in rats has been reported after injection into young litters of pooled blood from adult rats later used as donors,[14] and in dogs following massive transfusions.[15]

It is, therefore, just conceivable that if it were known that a newborn infant would certainly need some tissue graft later, such as an injection of marrow cells, and if a dependable donor were available such as a parent, some lasting tolerance for such cells might be secured by injecting living cells from the prospective donor within a day or two after birth. One can not assume, however, that the conditions observed in chickens or rodents will apply to man. Furthermore there are other difficulties and untoward results still to be surmounted.

Evidence has accumulated that a homograft, if it is retained, may inflict injury on the host.[16] This is well shown by the experiments of Billingham with isogenic strains of mice.[4] As already noted, a tissue graft to an F_1 hybrid from either parental strain is accepted, since all the antigens in the graft are present in the host and familiar to it. There are antigens (from the other parental strain) in the host, however, which are foreign to the graft and therefore "unfamiliar." If there are immunologically competent cells in the graft, mature lymphoid and plasma cells, these are stimulated to multiplication and fixed antibody formation, which injures the host more or less severely depending upon the degree of the antigenic differences determined by the histocompatibility genes not present in both tissues. This can be demonstrated with skin grafts and even better with grafts or transplantations of hematopoietic cells into very young recipients as in the production of tolerance.

If the antigenic differences were not too marked, the young mice grew normally and showed no obvious signs of illness, although their lymphoid tissue was distinctly hypoplastic. With other combinations after a week

[14] Ashley, F. L., Stein, H., Peterson, R., Grazer, F., and Longmire, L. P.: Tolerance induced by pooled antigen, Transplantation Bull. **5**: 29–30, incorporated in Plast. and Reconstruct. Surg. **22**, 1958.

[15] Peesa, A., and Gombos, A.: Acquired tolerance of skin homografts in dogs, Transplantation Bull. **5**: 30–32, incorporated in Plast. and Reconstruct. Surg. **22**, 1958.

[16] Trentin, J. J.: Tolerance and homologous disease in irradiated mice protected with homologous bone marrow, Ann. New York Acad. Sc. **73**: 799, 1958.

or more they stopped growing, had diarrhea, became emaciated, showed sparse ruffled fur and extensive involution of their lymphoid tissue, a condition termed "runt disease" by Billingham.[4] Such mice might die quickly or survive several weeks or more as chronically weak, stunted individuals. That this is caused by a reaction of the graft against the host is indicated by the facts (1) that the greater the antigenic differences, the more severe is the disease; (2) the disease is more severe if the donor has previously been sensitized with cells from the recipient; and (3) runt disease does not develop in a recipient which has received cells from an F_1 hybrid donor, since the latter finds no unfamiliar antigens in such a host and does not react against the host.

X-radiation is another measure which may be used to force acceptance of a homograft. The observations following injections of hematopoietic cells into heavily irradiated mice are of special interest because of their possible applicability to the treatment of human subjects.[16] If a properly adjusted fatal dose of x-radiation is given to an adult mouse, causing an arrest of multiplication or death of all its hematopoietic cells, the mouse will die within a few days if untreated. It will usually survive for a significant period if given an injection of living marrow or splenic cells. If these are isogenic, from an adult mouse of the same inbred strain, recovery is likely to be complete and permanent. If the injection is a homograft, from a mouse of a different strain, the animal recovers for a time, but after a few weeks an illness develops known as secondary radiation sickness or homologous disease, resembling the runt disease just described and often fatal. If heterologous (rat) cells are employed, life is still prolonged but the secondary radiation illness appears sooner and is more quickly fatal. In all cases the inoculated cells are found to settle out and proliferate in the corresponding organs of the host in the spaces vacated by the cells which were killed by the radiation or, in the infant mice, displacing some of the cells of the host. They become, at least temporarily, chimeras.

If a sublethal dose of radiation is administered, those cells of the host that survive eventually proliferate, react against the inoculated foreign cells and cause delayed illness that is often fatal. That this proliferation of the host's cells does not occur and cause illness in the heavily irradiated mice is indicated by the fact that such delayed illness is not seen if the cells inoculated are from an F_1 hybrid or if fetal cells (spleen or liver) are used. These latter, even if antigenically different, often become tolerant of their host. The use of fetal spleen or liver (but never mature lymphoid tissues) may thus prove of practical value in man for excessive radiation either accidentally or deliberately incurred, although the quantity of suitable fetal tissue available is obviously scanty. Fortunately it tolerates storage in a frozen state for substantial periods.

The behavior of larger mammals to grafts of marrow cells has been less extensively studied, but in general it is similar to that of rodents. In the

case of dogs this is well shown by recent reports of Thomas, Ferrebee et al.[17] Using beagles which were given a lethal radiation and then treated with homografts from a litter mate or from the mother, in 16 of 21 dogs there was evidence that function of the marrow was restored. The lymphoid tissues, however, were not adequately replaced, and although these 16 lived from two to 10 times as long as the controls which had a period of survival of six to 10 days, there was a heavy mortality from infections. In a later study of eight dogs [18] marrow was aspirated before radiation and was replaced soon afterward (autograft). All eight recovered, they showed progressive restitution of lymphoid as well as myeloid tissue, and all lived 39 days or more, six being in good health six months later. The fair success with homografts may be attributable perhaps to the use of a relatively pure if not inbred strain. Of five other radiated beagles treated with marrow from unrelated dogs, only one survived.

A few observations have been made on Rhesus monkeys with as yet inconclusive results. In a study of chimpanzees, Rothberg et al.[19] subjected eight animals to lethal radiation and then administered homologous marrow to six. One animal lived about six months but without evidence of any survival of the homologous marrow. The rest all died, treated and controls alike, within two to three weeks from hemorrhage and infections.

Relatively few observations of the fate of marrow homografts in man are recorded, and a large proportion of these have been patients with acute leukemia or advanced malignant neoplasms, situations which were not so well controlled or controllable as the animal experiments, making interpretation difficult. Homografts have been administered to a few patients who had accidentally been heavily radiated,[4] and eventually some information should be accumulated from such scattered subjects. Thomas et al.[20] have reviewed their observations covering homografts administered after heavy irradiation to seven patients, five of whom had acute leukemia. In two there was evidence of some multiplication of the inoculated cells but no real improvement occurred. In only one subject was there a clinical remission still maintained eight weeks after the radiation, but believed by them to be coincidental as far as the administration of marrow was concerned. All the others died from severe infections during the early period.

The almost invariable occurrence of severe infections during the period of immunologic paralysis following radiation, in very many cases not con-

[17] Thomas, E. D., Ashley, C. A., Lochte, H. L., Jr., Jaretzski, A., Jr., Sahler, O. D., and Ferrebee, J. W.: Homografts of bone marrow in dogs after lethal total body radiation, Blood **14**: 720–736, 1959.

[18] Mannick, J. A., Lochte, H. L., Jr., Ashley, C. A., Thomas, E. D., and Ferrebee, J. W.: Autografts of bone marrow in dogs after lethal total-body radiation, Blood **15**: 255–266, 1960.

[19] Rothberg, H., Blair, E. B., Gomez, A. C., and McNulty, W.: Observations on chimpanzees after whole body radiation and homologous bone marrow treatment, Blood **14**: 1302–1321, 1959.

[20] Thomas, E. D., Lochte, H. L., Jr., and Ferrebee, J. W.: Irradiation of the entire body and marrow transplantation: some observations and comments, Blood **14**: 1–23, 1959.

trolled by antibiotics or by the injected marrow, makes this at present a purely experimental and rather dubious procedure. The small rodents evidently have much greater resistance to infection after heavy radiation than do the dogs or primates. The occasional successes, however, even if only partial, warrant further study.

The procedure has been used with temporary success in several cases of acute leukemia in which marrow from an identical twin was administered, and therefore was genetically autologous. There was good immediate recovery and a remission of seven weeks before relapse in a case of Atkinson et al.,[21] and Thomas discussed two similar cases with good hematologic recovery.[22]

Tolerance can be temporarily increased and prolonged by adequate doses of cortisone and related steroids (but not by ACTH). This effect is gradually lost when the drugs have to be stopped.

The reaction leading to rejection of the grafts is related in some way to the production of plasma cells and to the plasma proteins. Favour [23] has pointed out that in those invertebrates in which homografts survive, there is no system of plasma cells and there are only traces of gamma globulin.

In patients with agammaglobulinemia, hereditary or acquired, there is also a remarkable absence of plasma cells.[11] There is a gross lack of capacity to produce antibodies in response to infections. They do not form isoagglutinins for red cells and do not react to mismatched transfusions. They can, however, develop the delayed type of cutaneous hypersensitivity. Successful homografts have been reported. Prolonged survival of homografts has also been noted in Hodgkin's disease, in which the development of delayed hypersensitivity is defective, although circulating antibodies are formed. The significance of these observations is not clear.

The same principles apply to transplantation of entire organs. The kidney has been a favorite experimental object. With current surgical technic it is easy to transplant a kidney to almost any area of the body of the same subject in which vascular anastomoses are feasible. A homograft from a different subject will usually function well for some days, particularly if the recipient's own kidneys have been removed, but after about a week secretion stops abruptly, the kidney shows edema, hemorrhages, interruption of circulation and eventually necrosis. There may be a multiplication of plasma cells in the grafted kidney while it is still viable, suggesting that the latter was reacting against its host.[24] The rejection was not altered by a presumably sublethal preliminary radiation of the host or of the kidney to

[21] Atkinson, J. B., Mahoney, F. J., Schwartz, I. R., and Hesch, J. A.: Therapy of acute leukemia by whole body irradiation and bone marrow transplantation from an identical twin, Blood **14**: 228–234, 1959.

[22] Thomas, E. D.: Discussion, Bone Marrow Transplantation Conference, Atlantic City, N. J., April 13, 1959, Blood **14**: 1254–1256, 1959.

[23] Favour, C. B.: Comparative immunology and phylogeny of homotransplantation, Ann. New York Acad. Sc. **73**: 590–595, 1958.

[24] Dempster, W. J.: Kidney homotransplantation, Brit. J. Surg. **40**: 447–465, 1952–53.

be grafted. Even if the host could be forced to tolerate the graft, the problem of possible injury to the host by the graft would still remain.

It is evident from this incomplete review that we are still far from a solution of the practical problem of utilizing homografts in human subjects. The immunologic processes which interfere seem to be quite fundamental, genetically determined, and universal among vertebrates. The prospects of favorably altering them at will are still distinctly dim. Much has been learned about the subject, however, and a few hints and suggestive leads obtained which well warrant continued study of this vitally important subject.

PAUL W. CLOUGH, M.D.

REVIEWS

Dietary Prevention and Treatment of Heart Disease. By JOHN W. GOFMAN, Ph.D., M.D., ALEX V. NICHOLS, Ph.D., and E. VIRGINIA DOBBIN, all of the University of California, Berkeley, California. 256 pages; 21 × 14 cm. G. P. Putnam's Sons, New York. 1958. Price, $3.95.

The authors discuss the nature of coronary heart disease, and conclude that excess in the fat-like substances in the blood of humans is indeed associated with increase in the development of arteriosclerosis and hence with increase of the risk of a future heart attack. The major sets of such particles which are important are defined by their speed of movement in the ultra-centrifuge. The risk of heart attacks is high, they believe, when the amounts of the S_f 0–12, S_f 12–20, S_f 20–100, or S_f 100–400 lipoproteins are high. It is important, they believe, to determine which of these groups of lipoproteins is elevated in a particular person. The level of the S_f 0–12 and the S_f 12–20 lipoproteins will fall and remain low so long as the person remains on a diet low in animal fats. A high level of S_f 20–100 or S_f 100–400 lipoprotein can be lowered by reducing the amount of carbohydrate in the diet, and these levels in general are not sensitive to the intake of animal or other fat in the diet. The authors believe that saturated fats are important and are related to atherosclerosis, whereas unsaturated fats have no intrinsic ability to reduce the blood lipids or inhibit arteriosclerosis, except insofar as a diet high in unsaturated fats is low in saturated fat.

Having developed this thesis, the authors then discuss the role of calories and overweight in the diet, and instruct the reader how to evaluate the composition of his present diet with regard to carbohydrates, proteins and saturated and unsaturated fats. This having been done, they describe in detail how to follow a recommended diet which, for example, for a caloric intake of 2,000 calories would consist of 100 grams of protein, 150 grams of carbohydrates, 85 grams of unsaturated fat, and 25 grams of highly saturated fat. The remainder of the book is composed of recipes designed to facilitate preparation of foods in accordance with their recommendations.

The authors' thesis is presented in detail since the effect of diet upon arteriosclerosis and on coronary disease is one subject to much debate at present. The authors differ with others in their view of the lack of intrinsic benefit of unsaturated fats. The recommended diet derives about half of its calories from fats, whereas others have suggested a lower proportion of fat calories.

The books is clearly and interestingly written, well-organized, and should be of interest to those who have to deal with the problem of diet and heart disease, and of use to those who recommend the type of dietary regulation which the authors advocate.

SIDNEY SCHERLIS, M.D.

Herz-Kreislauferkrankungen: Angewandte Physiologie und funktionelle Therapie. Band 1. Theoretische Grundlagen einer funktionellen Therapie (Kapitel I-VI). Band 2. Klinik und Therapie der Herz-Kreislauferkrankungen (Kapitel VII-XIV). By M. HOCHREIN and I. SCHLEICHER. 2,196 pages (both volumes; 24.5 × 17.5 cm. Dr. Dietrich Steinkopff Verlag, Darmstadt. 1959. Price, geb. DM 230.

The announced purpose of this extensive text and encyclopedia of cardiovascular disease is to provide the general practitioner with up-to-date information and in-

struction. The very great volume of information to be contained in such an ambitious undertaking requires precision, conciseness and balance.

Unfortunately, by 1959 standards, the presentation is too diffuse, lacks very significantly in some fields and is greatly outdated in others. The emphasis is too strongly directed toward the "neurogenic," "toxic" and numerous other mysterious or philosophical disorders rather than toward the significant cardiac disorders and their sound treatment. Programs of treatment as described appear as enormously complex, rather empirical, and very expensive to the practitioner, and as rather bewildering to the specialist. The cult of spa treatment is well documented with an apparently complete list of cardiovascular entities and fascinating specific indication for each. Similarly, dietotherapy, etc., is extensively discussed. On the other hand, auscultation, electrocardiographic, fluoroscopic and radiographic examination of the heart are inadequately dealt with. Many electrocardiograms are of technically poor quality and limited to three leads. Their interpretations can often be disagreed with.

For a text addressed to the practicing physician, the book contains too little information in too much space and is also not up to date. It is therefore impractical.

ARTHUR GRISHMAN, M.D.

Clinical Auscultation of the Heart. 2nd Ed. By SAMUEL A. LEVINE, M.D., F.A.C.P., and W. PROCTOR HARVEY, M.D. 657 pages; 25.5 × 17 cm. W. B. Saunders Company, Philadelphia. 1959. Price, $11.00.

This is the second edition of *Clinical Auscultation of the Heart,* ten years having elapsed since the first edition was published. There has been increased growth in the problems of auscultation during this time and with this has developed an increased appreciation of the significance of intelligent use of this diagnostic method.

This excellent presentation of the subject, by authors who have made many contributions in this field, is indispensable to students and to practicing physicians.

The authors have added numerous excellent illustrations in this edition and have incorporated the more recent advances in this very active field.

L. S.

Hypertension and Coronary Heart Disease: Classification and Criteria for Epidemiological Studies. First Report of the Expert Committee on Cardiovascular Diseases and Hypertension. World Health Organization: Technical Report Series No. 168. 28 pages; 24 × 16 cm. (paper-bound); also available in French and Spanish. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. 1959. Price, 30¢.

In October 1958, the World Health Organization Expert Committee on Cardiovascular Diseases and Hypertension met to discuss the public health problems created by cardiovascular disease. In the first report, the need for well planned epidemiological studies is stressed in order to establish the true frequency of coronary artery disease, hypertension, and related conditions in various countries. The committee suggests minimal criteria for the diagnosis of coronary artery disease and hypertension. Electrocardiographic criteria for the diagnosis of myocardial infarction and angina pectoris are also included as part of the suggested standardization in diagnosis.

The report is brief but lucid. The electrocardiographic criteria are generally acceptable although there are minor points of difference which many might suggest.

It is to be stressed that this is a report of an international group which carefully considers the problems of adequate epidemiological studies and the need for standardized classification and criteria. Adherence to the published criteria would enhance the value of data collected in different areas of the world by different teams of epidemiologists. Since many of the advances in the field of hypertensive cardiovascular disease and coronary artery disease will come from epidemiology, it is hoped that this short report will receive wide distribution and acceptance.

L. S.

Antibiotic Therapy for Staphylococcal Diseases. Antibiotics Monograph No. 12. Edited by HENRY WELCH, Ph.D., Editor-in-Chief of *Antibiotics and Chemotherapy* and *Antibiotic Medicine and Clinical Therapy*, Washington, D. C., and MAXWELL FINLAND, M.D., Associate Professor of Medicine, Harvard Medical School. 208 pages; 23.5 × 15.5 cm. Medical Encyclopedia, Inc., New York, N. Y. 1959. Price, $4.50.

This monograph, twelfth in a series on antibiotics published by Medical Encyclopedia, Inc., appears at a time when there is urgent need for a presentation of current concepts of the treatment of staphylococcal disease. Eight authors have contributed to this volume in which the accumulated experiences of numerous investigators in the management of staphylococcal infections have been summarized. Each contributor is an authority in the general field of chemotherapy and eminently qualified to present the subject which he has chosen. Furthermore, each author has had considerable personal experience with the antibiotic discussed.

The book is presented in seven chapters, one each dealing with erythromycin and its monopropionyl ester, oleandomycin, novobiocin, vancomycin, ristocetin and kanamycin. General aspects of the staphylococcal problem and early antibiotic therapy of staphylococcal infections are summarized by Dr. Welch in the first chapter. In the final section, Dr. Finland presents a recapitulation of the information covered in the text and discusses the basic principles governing therapy of staphylococcal infections.

Factors influencing the apparent increase and concentration of staphylococcal infections in hospital environments have been presented very clearly. The high incidence is noted of a few phage types of staphylococci suggesting that this problem is of the nature of a pandemic. Finally, the increased awareness of the problem is attributed to better methods of analyzing hospital records, improvement of laboratory technics and a marked decline in the incidence of many other bacterial infections formerly associated with high morbidity and mortality. An attempt has been made to present the available facts objectively, there being a deliberate de-emphasis of the oft quoted concept that the staphylococcal problem is a hopeless one. The importance of proper choice and proper use of antibiotics as well as all other supportive therapeutic methods is stressed. Although there is not general agreement on the antibiotics best suited to the treatment of staphylococcal infections, the consensus seems to support the view that polyvalent therapy is indicated. With this the reviewer would concur. Finally, the importance of restricting the use of certain antistaphylococcal drugs in each hospital environment is emphasized.

This monograph is a well written, up to date account of staphylococcal disease therapy. It should be read by every physician who treats patients with staphylococcal disease and by all laboratorians whose responsibility it is to provide adequate microbiological support for the study of these problems.

FRED R. MCCRUMB, JR., M.D.

Tuberculosis and other Communicable Diseases. Edited by J. ARTHUR MYERS, M.D., Professor of Internal Medicine and Public Health, Medical, Public Health and Graduate Schools, University of Minnesota. 499 pages; 23.5 × 16 cm. Charles C Thomas, Publisher, Springfield, Illinois. 1959. Price, $14.50.

Twenty-five physicians, all specialists in the field of infectious diseases or preventive medicine, have contributed to this book edited by Dr. Myers. The book has been designed to appeal to the student and practitioner of medicine as well as nurses and public health workers. It is the hope of the editor that the general point of view expressed in this book will further the cause of prevention and control of communicable diseases.

Discussions have been limited for the most part to those infectious diseases which are contagious. Certain maladies such as encephalitis of the arthropod-borne type, cat-scratch fever, brucellosis and systemic mycoses and some forms of bacterial meningitis have been included in the text in spite of the generally held view that they are not communicable from one human host to another. Indeed it is not clear what criteria were employed in the selection of topics to be covered in this book.

One must assume that the format followed in each of the chapters is an editorial suggestion made for the sake of brevity. Unfortunately, condensation of information has not been accomplished with equal skill in all of the sections. Excellent selection of material has been made in the case of the chapters dealing with pertussis, rubella, rubeola, varicella, variola and the enteric disorders. Omission of adequate discussions of immunization against such diseases as diphtheria and poliomyelitis seems to represent a gross defect in a book which is intended to stress the importance of communicable disease control. Generally, the presentations are oversimplified and, in the opinion of the reviewer, are not adequate as guides for medical students or practitioners of medicine. Exceptions to this comment have been noted above.

Abbreviated bibliographies represent another inadequacy of the book, the extreme examples being a single reference to a recent monograph on brucellosis at the end of the chapter dealing with this disease and no references following a very superficial discussion of the encephalitides. Editorial accuracy has not been assessed by the reviewer in minute detail, however; in one bibliography containing 48 references, at least five authors' names have been misspelled.

It is the opinion of the reviewer that this book as a reference work will find keen competition from several other recent volumes dealing with infectious diseases.

FRED R. MCCRUMB, JR., M.D.

Xylocaine: The Pharmacological Basis of Its Clinical Use. By STEN WIEDLING. 146 pages; 21 × 13.5 cm. Almqvist & Wiksell, Stockholm, Sweden. 1959. Available to physicians in this country on a complimentary basis from Astra Pharmaceutical Products, Inc.; when their supply has been exhausted, book will be available from the original publishers, Almqvist & Wiksell, Stockholm, Sweden, at $4 per copy.

Of the many local anesthetic agents available, not any in recent years has received the general acceptance by the medical profession as has Xylocaine. Since its introduction more than a decade ago, it has become an active competitor of the long established procaine hydrochloride.

This treatise gives the historical background leading to the synthesis of Xylocaine and its early clinical trials. Another section of the book is concerned with the mechanism of action of local anesthetics at a cellular level. Pharmacologic pro-

cedures for the evaluation of local anesthetics are discussed and their relative merits delineated.

The complete pharmacologic profile of Xylocaine is discussed in subsequent chapters. The toxicity of the agent to various organ systems is also reviewed.

This treatise contains many descriptive graphs that give at a glance the relative potencies and toxicities of the generally used local anesthetics. The style is concise and in this one volume succintly summarizes the more than 400 scientific publications dealing with Xylocaine. An excellent bibliography is appended.

JOHN C. KRANTZ, JR.

Safe Handling of Radioactive Isotopes in Medical Practice. By EDITH H. QUIMBY, Sc.D., Professor of Radiology (Physics), College of Physicians and Surgeons, Columbia University. 129 pages; 21.5 × 14.5 cm. The Macmillan Company, New York. 1960. Price, $4.50.

The author has performed a great service for her medical colleagues by writing this valuable reference guide for anyone involved in the use of radioisotopes in medical practice. If used as a supplement to the earlier and more complete volume by Dr. Quimby, entitled *Radioactive Isotopes in Clinical Practice,* the true value of this concise yet complete volume may be seen.

The book consists of eight chapters dealing with such problems as the nature of radioactivity; diagnostic and therapeutic uses of radioisotopes; patient care instructions following administration of radioisotopes and precautions in the hospital and the "hot" laboratory. In addition, there are discussions of methods of dealing with radioactive contamination and disposal of radioactive wastes, all practical points for the hospital radioisotope unit.

Eight appendices are included, covering physical data for some radioisotopes used in medical diagnosis and therapy; radioactive content of patients at various time periods after a dose of radioactive material, and a section devoted to useful reference books. A short subject index completes the book.

The book seems to be modestly priced and should be of genuine help to anyone responsible for the safe use of radioactive isotopes in medicine today.

J. B. W.

Atlas of Human Anatomy. 5th Ed. By FRANZ FROHSE, MAX BRÖDEL, and LEON SCHLOSSBERG. 180 pages; 21 × 13.5 cm. Barnes & Noble, Inc., New York, N. Y. 1959. Price, $2.95 paper; $4.50 cloth.

This fifth edition of the Frohse-Brödel atlas is not actually an atlas but a very elementary textbook of human anatomy. For many years the illustrations were reproduced as large-sized charts which were later modified and increased in number by Max Brödel. It changed from an atlas to a text of anatomy when Dr. Samuel Smith wrote an explanatory text which was edited by Dr. Ashley Montagu. As a textbook, it is elementary. It is, in fact, the type of material that a student should know before entering medical school. It would be ideal for laymen who wish to become superficially acquainted with anatomy. It would perhaps be of some value for a book of anatomy for nurses. The anatomical illustrations are well executed and printed in color but the coverage of the body is very incomplete. In many instances the illustrations try to depict so much in a very small illustration that it is difficult to distinguish one part from another. The illustrations that have to do with the sex functions have been covered in somewhat greater detail.

F. H. J. F.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Acid Mucopolysaccharides in the Female Genital System and Their Rôle in the Mechanism of Ovulation. (Acta Endocrinologica, *Supplementum 47.*) By FRANCIS ZACHARIAE; translated from the Danish by ANNA LA COUR, née CLAESSEN, and with a summary in Danish. 64 pages; 24.5 × 16 cm. (paper-bound). 1959. Periodica, Copenhagen. Price, Danish Kroner 12,00 ($1.75).

Anorexia Nervosa: Its History, Psychology, and Biology. A Psychosomatic Medicine Monograph. By EUGENE L. BLISS, M.D., Associate Professor of Psychiatry, University of Utah College of Medicine; and C. H. HARDIN BRANCH, M.D., Professor and Head of the Department of Psychiatry, University of Utah College of Medicine. 210 pages; 24 × 16 cm. 1960. Paul B. Hoeber, Inc., Medical Division of Harper & Brothers, New York. Price, $5.50.

Basic Facts of Body Water and Ions. By STEWART M. BROOKS, M.S., Science Instructor, Lasell Junior College, Auburndale, Massachusetts, etc. 159 pages; 21 × 14 cm. (paper-bound). 1960. Springer Publishing Company, Inc., New York. Price, $2.75.

Care of Children in Hospitals. By the COMMITTEE ON HOSPITAL CARE OF THE AMERICAN ACADEMY OF PEDIATRICS. 96 pages; 23 × 15 cm. (paper-bound). 1960. American Academy of Pediatrics, Evanston, Illinois. Price, $1.50.

The Central Nervous System and Behavior: Translations from the Russian Medical Literature, Collected for the Participants of the Third Macy Conference on the Central Nervous System and Behavior, Held Under the Joint Sponsorship of The Josiah Macy, Jr. Foundation, The National Science Foundation, Princeton, New Jersey, February 21–24, 1960. 1,051 pages; 27 × 20.5 cm. (paper-bound, loose-leaf). 1960. U. S. Department of Health, Education, and Welfare, Public Health Service; prepared and distributed by the Russian Scientific Translation Program, National Institutes of Health, Bethesda, Maryland. No charge.

Children of Alcoholic Fathers. (Acta Paediatrica, *Vol. 49, March 1960, Suppl. 121.*) From the Child Psychiatric Department of Karolinska Institutet at Kronprinsessan Lovisas Barnsjukhus (Head: PROFESSOR SVEN AHNSJÖ), Stockholm, Sweden. By INGVAR NYLANDER; translated by BASIL and DOROTHY FINER. 134 pages; 24.5 × 16 cm. (paper-bound). 1960. Almqvist & Wiksells Boktryckeri AB, Uppsala. Price, Swed. kr. 25.–

Clinical Endocrinology. I. Edited by EDWIN B. ASTWOOD, M.D. 724 pages; 23.5 × 15.5 cm. 1960. Grune & Stratton, New York. Price, $18.75.

Communicable and Infectious Diseases: Diagnosis, Prevention, Treatment. 4th Ed. By FRANKLIN H. TOP, A.B., M.D., M.P.H., F.A.C.P., F.A.A.P., F.A.P.H.A., Professor and Head, Department of Hygiene and Preventive Medicine, State University of Iowa, Iowa City, Iowa, etc.; and collaborators. 812 pages; 25.5 × 17 cm. 1960. The C. V. Mosby Company, St. Louis. Price, $20.00.

Dental Care: Interval and Frequency of Visits, United States, July 1957–June 1959. Statistics on Time Interval Since Last Dental Visit and Frequency of Dental

Visits During a Year by Age, Sex, Residence, Region, Race, Income, and Education. Based on Data Collected in Household Interviews During July 1957–June 1959. Health Statistics from the U. S. National Health Survey. Public Health Service Publication No. 584–B14. 42 pages; 26 × 20 cm. (paper-bound). 1960. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 35¢.

Dental Care: Volume of Visits, United States, July 1957–June 1959. Statistics on Volume of Dental Visits by Type of Dental Service, Age, Sex, Residence, Region, Race, Income, and Education. Based on Data Collected in Household Interviews During the Period July 1957–June 1959. Health Statistics from the U. S. National Health Survey. Public Health Service Publication No. 584–B15. 45 pages; 26 × 20 cm. (paper-bound). 1960. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 35¢.

Dermatologic Medications. 2nd Ed. By MARGUERITE RUSH LERNER, M.D., Clinical Instructor, Section of Dermatology, Department of Medicine, Yale University School of Medicine; and AARON BUNSEN LERNER, M.D., Ph.D., Professor and Head of Section of Dermatology, Department of Medicine, Yale University School of Medicine. 208 pages; 20.5 × 13.5 cm. 1960. The Year Book Publishers, Inc., Chicago. Price, $6.00.

Epidemiology of Cancer of the Lung: Report of a Study Group. World Health Organization Technical Report Series No. 192. 13 pages; 24 × 16 cm. (paper-bound). 1960. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Epidemiology of Mental Disorders: Eighth Report of the Expert Committee on Mental Health. World Health Organization Technical Report Series No. 185. 29 pages; 24 × 16 cm. (paper-bound). 1960. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Evaluation and Presentation of Spectro-analytical Results. By A. B. CALDER, B.Sc., Ph.D., F.R.I.C., F.I.S., Senior Lecturer in Inorganic Chemistry, Rutherford College of Technology, Newcastle-upon-Tyne. 47 pages; 16.5 × 10.5 cm. (paper-bound). 1960. The Macmillan Company, New York. Price, $1.25.

Expert Committee on Leprosy: Second Report. World Health Organization Technical Report Series No. 189. 27 pages; 24 × 16 cm. (paper-bound). 1960. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

First Aid: Diagnosis and Management. 5th Ed. By WARREN H. COLE, Professor and Head of the Department of Surgery, University of Illinois College of Medicine, etc.; and CHARLES B. PUESTOW, Clinical Professor of Surgery, University of Illinois College of Medicine and Graduate School, etc.; with 16 contributing authors. 420 pages; 21.5 × 14 cm. 1960. Appleton-Century-Crofts, Inc., New York. Price, $6.25.

From Fish to Philosopher: The Story of Our Internal Environment. By HOMER W. SMITH; supplement with collaboration of CIBA PHARMACEUTICAL PRODUCTS INC. 304 pages; 18.5 × 11 cm. (paper-bound). 1959. Ciba Pharmaceutical Products, Inc., Summit, N. J. No charge.

The Haemolytic Anaemias, Congenital and Acquired. Part I: The Congenital Anaemias. 2nd Ed. By J. V. DACIE, M.D. (Lond.), F.R.C.P. (Lond.), Professor of Haematology, University of London (Postgraduate Medical School of London). 339 pages; 22.5 × 14.5 cm. 1960. Grune & Stratton, New York. Price, $7.00.

Heart Conditions and High Blood Pressure Reported in Interviews, United States, July 1957–June 1958. Statistics on the Prevalence of Heart Conditions and High Blood Pressure and Days of Disability Due to These Conditions by Age, Sex, and Medical Care Status. Based on Data Collected in Household Interviews During the Period July 1957–June 1958. Health Statistics from the U. S. National Health Survey. Public Health Service Publication No. 584–B13. 36 pages; 26 × 20 cm. (paper-bound). 1960. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 30¢.

International Work in Leprosy, 1948–1959. (Reprinted from *WHO Chronicle* 1960, *14*, 2–39.) 39 pages; 24 × 18 cm. (paper-bound). 1960. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Intraärterial Infusion of Procaine in Therapeutic Practice. By N. K. GORBADEI; with a supplement, *The Treatment of Patients with Hypertension by Intra-arterial Infusion of Procaine Solution,* by I. I. VELIKANOV; translated from Russian. 135 pages; 23.5 × 15.5 cm. 1960. Consultants Bureau, Inc., New York. Price, $7.50.

A Manual of Tropical Medicine. 3d Ed. By GEORGE W. HUNTER, III, Ph.D., Col. U. S. A. (Ret.), Lecturer in Microbiology, College of Medicine and Biological Sciences, University College, University of Florida, Gainesville, Florida, etc.; WILLIAM W. FRYE, Ph.D., M.D., Sc.D. (Hon.), Professor of Tropical Medicine, Dean, School of Medicine, and Vice-President, Louisiana State University, New Orleans, etc.; and J. CLYDE SWARTZWELDER, Ph.D., Professor of Medical Parasitology, Louisiana State University, School of Medicine, New Orleans, Louisiana, etc. 892 pages; 24 × 16 cm. 1960. W. B. Saunders Company, Philadelphia. Price, $15.00.

Medical Care of the Adolescent: A Textbook Concerning the Medical Care and Understanding of Adolescents Themselves and of their Disorders. By J. ROSWELL GALLAGHER, M.D., Chief of the Adolescent Unit, The Children's Hospital Medical Center, Boston, etc.; and THE STAFF PHYSICIANS OF THE ADOLESCENT UNIT. 384 pages; 24 × 16 cm. 1960. Appleton-Century-Crofts, Inc., New York. Price, $10.00.

Metal-Binding in Medicine: Proceedings of a Symposium Sponsored by Hahnemann Medical College and Hospital, Philadelphia. MARVIN J. SEVEN, Editor; L. AUDREY JOHNSON, Associate Editor. 400 pages; 26 × 18.5 cm. 1960. J. B. Lippincott Company, Philadelphia. Price, $13.75.

Microscopie Electronique. L'Hepatocyte Humain, Normal et Pathologique. By JACQUES IZARD. 164 pages; 24.5 × 16 cm. (paper-bound). 1960. Librairie Arnette, Paris. Price, Broché 25 N.F.

Pediatric Anesthesiology. 2nd Ed. By M. DIGBY LEIGH, M.D., Associate Professor of Surgery (Anesthesia), University of Southern California, etc.; and M. KATHLEEN BELTON, M.D., Assistant Professor of Surgery (Anesthesia), University of Southern California, etc.; in collaboration with GEORGE B. LEWIS, JR., M.D., and EDWARD B. SCOTT, M.D., Assistant Attending Anesthesiologists, Childrens Hospital of Los Angeles. 461 pages; 24 × 15.5 cm. 1960. The Macmillan Company, New York. Price, $12.00.

Physiology of Prematurity: Transactions of the Fourth Conference, March 25, 26 and 27, 1959, Princeton, N. J. Edited by JONATHAN T. LANMAN, M.D., Department of Pediatrics, New York University-Bellevue Medical Center, New York, N. Y. 187 pages; 23.5 × 16 cm. 1960. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $4.50.

Physiology of the Retina and the Visual Pathway. Monographs of the Physiological Society, Number 6. (Editors: H. BARCROFT, L. E. BAYLISS, A. L. HODGKIN.) By G. S. BRINDLEY, M.A., M.D., Fellow of King's College and Lecturer in Physiology in the University of Cambridge. 298 pages; 22.5 × 14.5 cm. 1960. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price, $7.50.

Problemès de Réanimation: Compte Rendu de Rapports, Communications et Discussions Publié sous la Direction du PROFESSEUR P. MICHON *et du* PROFESSEUR AGRÉGÉ A. LARCAN. *Journées de Réanimation Medico-Chirurgicale, Nancy—25 et 26 Avril 1959.* 405 pages; 25.5 × 16.5 cm. (paper-bound). 1959. G. Doin & Cie., Paris. Price, 30 NF.

Science and Engineering in American Industry: Report on a 1956 Survey. Prepared for the National Science Foundation by the U. S. Department of Labor, Bureau of Labor Statistics (NSF 59–50). 117 pages; 26 × 20 cm. (paper-bound). 1959. A publication of the National Science Foundation, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 70¢.

A Study of Special Purpose Medical-History Techniques. A Methodological Study of Special Purpose Medical-History-Taking Procedures Applicable to Population Surveys Based on Health Examinations. Health Statistics from the U. S. National Health Survey. Public Health Service Publication No. 584–D1. 27 pages; 26 × 20 cm. (paper-bound). 1960. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 30¢.

Tejido Conectivo y Enfermedades del Colageno. By MARIO F. VILLAMIL and ROBERTO E. MANCINI; preface by PROFESOR MANUEL E. VARELA. 379 pages; 23.5 × 16 cm. (paper-bound). 1959. Lopez & Etchegoyen, S.R.L., Buenos Aires.

Virus Virulence and Pathogenicity: Ciba Foundation Study Group No. 4, in honour of Prof. J. Mulder. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., M.R.C.P., and CECILIA M. O'CONNOR, B.Sc. 114 pages; 19 × 13 cm. 1960. Little, Brown and Company, Boston. Price, $2.50.

ERRATUM

Reference is made to the following article:

Morgenstern, L. L.: Some observations on the use of chlorpropamide in primary tolbutamide-failure diabetics, Ann. Int. Med. **52**: 761–772 (Apr.) 1960.

In the above article, wherever "gamma%" is printed, it should be corrected to "gamma per milliliter."

MEDICAL NEWS

American College of Physicians Research Fellowships

It was voted at the April meeting of the Board of Regents in San Francisco on the recommendation of the Committee on Fellowships and Scholarships to approve a change in Research Fellowships given by the College. There will be no one-year College Research Fellowships other than those already awarded last November for the academic year July 1, 1960 to June 30, 1961. It is believed that a much greater contribution will be made by the College with the establishment of three-year Research Fellowships, although for the time being the total number of fellowships will be relatively few. Applications may be received, however, for two Research Fellowships to be awarded for a term of three years.

The purpose of such three-year fellowships shall be stated as that of further developing in young physicians a major interest in research in any science basic to medicine or in medical education, or both. Furthermore, it is to be stipulated that the recipient of such a fellowship shall devote a minimum of 80 per cent of his time to research, regardless of the type of appointment that he holds in any given institution.

Applications for the recipients of such fellowships shall be made by the Chairman of the Department of Medicine in any institution in the United States and Canada with a recognized program of medical education and research. The Chairman of the Department of Medicine in any such institution shall be responsible for presenting a careful and complete evaluation of any such individual whom he wishes to recommend for such a College Fellowship. Such recommendation shall be further implemented by a letter from the Governor of the State or Province concerned. Not more than one name may be recommended by any Chairman of a Department of Medicine in any given institution in any calendar year.

Applications for such Research Fellowships may be made only on behalf of physicians who are citizens of the United States or Canada and who have completed an internship in an approved hospital and have had at least two years of approved residency training, preferably with a third year of residency or a year of research training.

The Chairman of the Department who sponsors a given applicant must be prepared to provide adequate facilities for the recipient of this fellowship during the course of his fellowship, or to help him to obtain such facilities in an institution in which research is to be carried out. If the recipient is to carry on his research in an institution other than the one from which the initial application is made, the grant for such work elsewhere will follow the recipient.

Such research grants will be made by the College to start on July 1 of any given year, unless for satisfactory reasons a necessary and proper delay is requested.

On March 1 of the first and second calendar years following the grant of a research fellowship a report of progress shall be required from the recipient of the award and from the Chairman of the Department who made the original application and recommendation. Renewal of the grant at the end of the first and second twelve-month periods will be contingent upon the receipt of reports of progress satisfactory to the Committee on Fellowships and Scholarships. A final report at the end of the third year of fellowship will also be required from the recipient and from his preceptor.

For further information write

Edward C. Rosenow, Jr., M.D.
Executive Director
American College of Physicians
4200 Pine Street
Philadelphia 4, Pa.

American College of Physicians Scholarships

Mead Johnson Residency Scholarships

These scholarships are designed to aid deserving young physicians planning careers in the specialty of internal medicine and are financed by Mead Johnson & Company.

The nominee must be in his internship or residency period, with some preference to residents. He must intend to practice internal medicine. He must appear to possess attributes for success in the practice of internal medicine. He must need funds to attain his goal of adequate education in internal medicine.

Ten such awards are made annually. The stipend for each is $1,000.00. Applications must be filed with the Executive Offices of the College, 4200 Pine Street, Philadelphia 4, Pa., not later than October 1 each year. Selections will be made at the mid-November meeting of the Board of Regents, and scholarships begin the following July 1.

Traveling Scholarships

The aim of these scholarships is to provide an opportunity for worthy, young physicians, preferably Associates of the College, to spend a month, more or less, as visiting fellows at some institution, or institutions, for observation and postgraduate study. The Committee on Fellowships and Scholarships of the College facilitates opportunities for these scholarships at outstanding institutions where a month's observation, contact and study will be an exceptional inspiration and a practical source of training. The income, approximately $400.00 each, is used for payment of travel expenses, in whole or in part. Recipients are chosen and institutions designated by the Committee on Fellowships and Scholarships, subject to approval by the Board of Regents.

The A. Blaine Brower Traveling Scholarships:

There are two of these fellowships, the first having been initiated through a grant by Dr. A. Blaine Brower, F.A.C.P., of Dayton, Ohio; the second A. Blaine Brower Traveling Scholarship was added by the Board of Regents.

The Elizabeth Archbold Bowes Traveling Scholarship:

The first scholarship, established through an annual grant by Mrs. Margaret Bowes Murphy, Chicago, Ill., in memory of her mother, and administered on the same basis as the Brower Traveling Scholarships. However, the Bowes Traveling Scholarship is restricted to candidates from Canada.

The Willard O. Thompson Memorial Traveling Scholarship:

First annual scholarship, established by the late Dr. Thompson's widow, Dr. Phebe Thompson, and by friends of Dr. Thompson. It is particularly directed toward the field of endocrinology, the specialty in which Dr. Thompson was most interested. It is administered on the same bases as the Brower Traveling Scholarships.

Interested Associates of the College shall file application on or before October 15 each year; recipients will be selected by the Committee on Fellowships and Scholarships and the Board of Regents at their mid-November meeting. Scholarships will be arranged to start after the following January 1, at the convenience of the recipient and of the preceptor or institution.

Applications may be obtained from the Executive Director of the College.

The Glorney-Raisbeck Fellowship

The New York Academy of Medicine has announced that the Glorney-Raisbeck Fellowship in the Medical Sciences will be awarded for one year of research or study in any field of medicine or its allied sciences. The initial award will be for the academic year beginning July 1, 1961. The fellowship is renewable on a year-to-year basis for two additional years. It carries a stipend of $5,000 and is open only to M.D.'s who have "demonstrated potential for productivity in research and teaching." Candidates must assure the Committee on Medical Education of an institution in which to carry on their projects. For information contact Dr. Aims C. McGuinness, Executive Secretary, Committee on Medical Education, The New York Academy of Medicine, 2 E. 103 St., New York 29, N. Y.

Examinations and Licensure

American Board of Pediatrics: Written, New York City, January, 1961. Final date on filing application is Dec. 1. Administrative Sec., Mrs. Eleanor J. Mitchell, Rosemont, Pa.

American Board of Psychiatry and Neurology: New York, New York, Dec. 12–13. Child Psychiatry, Chicago, April 25–26. Sec., Dr. David A. Boyd, Jr., 102–110 Second Ave., S.W., Rochester, Minn.

Future Meetings

Aug. 14–19—International Congress of Clinical Chemistry at Edinburgh, Scotland. Dr. S. C. Frazer, Clinical Laboratory, Royal Infirmary, Edinburgh, Scotland.

Aug. 21–26—The Third International Congress of Physical Medicine at Washington, D. C. Headquarters: Mayflower Hotel. Exec. Sec., Dorothea C. Augustin, 30 North Michigan Avenue, Chicago 2, Ill.

Aug. 28–Sept. 1—International Congress for Individual Psychology at Vienna, Austria. Dr. Walter Spiel, Neuropsychiatric Clinic, Vienna 9, Lazarettgasse 14, Austria.

Sept. 1–3—International Congress of Nephrology in Geneva and Evian, France. Prof. G. Richet, Hospital Necker, 149, rue de Sevres, Paris 15e, France.

Sept. 1–7—International Congress of Nutrition at Washington, D. C. Dr. Milton O. Lee, 9650 Wisconsin Ave., Washington 14, D. C., General Secretary.

Sept. 4–10—International Society of Hematology, Tokyo, Japan. Dr. James L. Tullis, Suite 6 D, 1180 Beacon St., Brookline 46, Mass., Secretary-General, Western Hemisphere.

Sept. 7–10—Medical Women's International Association at Baden-Baden, Germany. Dr. Grete Albracht, Heilwigstr. 12, Hamburg 20, Germany, President.

Sept. 12–15—International Society of Blood Transfusion at Tokyo, Japan. Headquarters: Nihon Toshi Center, Hirakawacho, Chiyoda-Ku. Dr. Seizo Murakami, Blood Transfusion Research Laboratory, Japanese Red Cross Society, Shibuya, Tokyo, Secretary-General.

Sept. 13–15—The Fourth National Cancer Conference of the American Cancer Society and the National Cancer Institute at Minneapolis, Minn. Coördinator: Roald N. Grant, M.D., American Cancer Society, Inc., Medical Affairs Department, 525 West 57th Street, New York 1, N. Y.

Sept. 15–22—World Medical Association, at West Berlin, Germany. Headquarters: Berlin-Hilton Hotel. Dr. Louis H. Bauer, 10 Columbus Circle, New York 19, N. Y., Executive Secretary.

Sept. 18–21—International Meeting of Forensic Pathology, New York City. Dr. Milton Helpern, 55 E. End Avenue, New York 28, N. Y.

Sept. 22–26—International Cancer Cytology Conference, Madrid, Spain. Miss Elizabeth L. Hughes, 3007 Salzedo, Coral Gables, Fla., Corresponding Secretary.

Sept. 29–Oct. 1—Fourth Scientific Meeting of the Society of Social Medicine at Oxford, England. Headquarters: Oxford University. Dr. Alice M. Stewart, Department of Social Medicine, 8, Keble Road, Oxford, England, Secretary.

October 2–4—First International Symposium of Cybernetic Medicine at Naples, Italy. Professor Renato Vinciguerra, Via Roma, 348-Naples, Italy, S.I.M.C. Secretary.

Oct. 5–8—American Academy for Cerebral Palsy, Pittsburgh, Pa. Headquarters: Penn-Sheraton Hotel. Dr. Joseph D. Russ, 1520 Louisiana Ave., New Orleans 15, La., Executive Secretary.

Oct. 11–12—Congress on Industrial Health at Charlotte, N. C. Headquarters: Hotel Charlotte. Council on Occupational Health, American Medical Association, 535 N. Dearborn St., Chicago 10, Ill.

Oct. 13–15—Academy of Psychosomatic Medicine, at Philadelphia, Pa. Headquarters: Benjamin Franklin Hotel. Dr. Mertram B. Moss, 55 E. Washington, Chicago 2, Ill.

Oct. 21–25—American Heart Association, Inc., at St. Louis, Mo. Headquarters: Jefferson Hotel. Mr. Rome A. Betts, 44 E. 23rd St., New York 10, N. Y., Executive Director.

Oct. 23–29—The Seventh Panamerican Congress of Gastroenterology in Santiago, Chile. Congress Office, Dr. Ricardo Katz, Hospital del Salvador, Casillar 70–D, Santiago, Chile.

Oct. 26–27—Industrial Hygiene Foundation of America, Inc., at Pittsburgh, Pa. Headquarters: Mellon Institute. Dr. H. H. Schrenk, 4400 Fifth Ave., Pittsburgh 13, Pa., Managing Director.

Oct. 31–Nov. 3—Interstate Postgraduate Medical Association of North America at Pittsburgh, Pa. Headquarters: Pittsburgh-Hilton Hotel. Mr. Roy T. Ragatz, Box 1109, Madison 1, Wis., Executive Director.

Oct. 31–Nov. 2—Association of American Medical Colleges at Hollywood Beach, Fla. Headquarters: Diplomat Hotel. Dr. Ward Darley, 2530 Ridge Ave., Evanston, Ill., Executive Director.

Nov. 2–5—American Society of Tropical Medicine and Hygiene at Los Angeles, Calif. Headquarters: Biltmore Hotel. Dr. Rolla B. Hill, 3575 St. Gaudens Rd., Miami 33, Fla., Executive Secretary.

Nov. 16–18—International Symposium on the Etiology of Myocardial Infarction at Detroit, Mich. Headquarters: Henry Ford Hospital. Dr. Thomas N. James, Henry Ford Hospital, Detroit 2, Mich., Chairman, Section on Cardiovascular Research.

Nov. 29–Dec. 2—The American Medical Association Clinical Meeting at Washington, D. C.

Nov. 30–Dec. 3—Canadian Heart Association and National Heart Foundation of Canada, Joint Annual Meeting at Toronto, Ont., Canada. Headquarters: Royal York Hotel. Dr. John B. Armstrong, National Heart Foundation, 501 Yonge St., Toronto 5, Canada.

Dec. 4–9—Radiological Society of North America at Cincinnati, Ohio. Headquarters: Netherland Hilton Hotel. Dr. Donald S. Childs, 713 E. Genessee St., Syracuse 2, N. Y., Secretary.

Post Graduate Education

Aug. 8–20—Medical Genetics. Members of the Laboratory and faculty of Johns Hopkins University School of Medicine will conduct this course at Bar Harbor, Maine. For information contact Dr. Victor A. McKusick, Johns Hopkins Hospital, Baltimore 5, Maryland; and Dr. John L. Fuller, Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine.

Aug. 11–13—Medical Statistics. University of Colorado Medical Center, Denver, Colo.

Aug. 24—Arthritis and Rheumatism. University of California at Los Angeles. Fees to be announced. For information contact Department of Continuing Education in Medicine and Health Sciences, U.C.L.A. Medical Center, Los Angeles 24, Calif.

Aug. 31–Sept. 6—Pediatrics. University of Colorado Medical Center, Estes Park, Colo.

Oct. 3–May 31, 1961—Cardiovascular Disease. Harvard Medical School, Boston, Mass. Fee $800. For information contact Assistant Dean, Courses for Graduates, Harvard Medical School, Boston 15, Mass.

Oct. 27–29—Postgraduate Gastroenterology, at Philadelphia, Pa. Headquarters: Bellevue-Stratford Hotel. For information contact American College of Gastroenterology, 33 West 60th St., New York, 23, N. Y.

Nov. 28–Dec. 2—Coronary Artery Disease at the Texas Medical Center, Houston, Texas. $5.00 registration fee for those desiring AAGP Category I credit. For information contact Dean, The University of Texas Postgraduate School of Medicine, 410 Jesse Jones Library Bldg., Texas Medical Center, Houston 25, Texas.

Department of Health, Education, and Welfare

Communicable Disease Center

Atlanta 22, Georgia

Schedule of Laboratory Refresher Training Courses

October 1960—June 1961

Dates	Courses	Duration
Oct. 10–21	Fundamentals of Virology (819)	2 wks.
Oct. 31–Nov. 11	Laboratory Methods in the Diagnosis of Tuberculosis (855)	2 wks.
Nov. 28–Dec. 2	Laboratory Methods in the Diagnosis of Rabies (826)	1 wk.
Dec. 5–9	Bacteriophage Typing of Staphylococci (856)	1 wk.
Jan. 9–Feb. 3	Laboratory Methods in Medical Mycology (815)	4 wks.
Jan. 23–Feb. 10	Serologic Methods in Microbiology (941)	3 wks.
Jan. 30–Feb. 10	Laboratory Methods in the Diagnosis of Tuberculosis (855)	2 wks.
Feb. 13–24	Laboratory Methods in the Study of Pulmonary Mycoses (817)	2 wks.
Feb. 27–Mar. 17	Laboratory Methods in Medical Bacteriology (838)	3 wks.
Mar. 6–10	Laboratory Diagnostic Methods in Veterinary Mycology (940)	1 wk.

Dates	Courses	Duration
Mar. 13–31	Laboratory Methods in the Diagnosis of Viral and Rickettsial Diseases (820)	3 wks.
Mar. 20–24	Special Problems in Medical Bacteriology (839)	1 wk.
Mar. 27–Apr. 7	Laboratory Methods in Enteric Bacteriology (850)	2 wks.
Apr. 3–7	Laboratory Methods in the Diagnosis of Rabies (826)	1 wk.
**	Laboratory Methods in the Diagnosis of Malaria (805)	1 wk.
**	Special Training in Virus Techniques (821)	2–4 wks.
**	Typing of *Corynebacterium diphtheriae* (842)	1 wk.
**	Special Problems in Enteric Bacteriology (851)	2 wks.
**	Phage Typing of *Salmonella typhosa* (852)	1 wk.
**	Laboratory Methods in the Diagnosis of Leptospirosis (853)	1–4 wks.
**	Serologic Differentiation of Streptococci (854)	2 wks.
**	Special Problems in Microbiology (942)	1–2 wks.

** Courses given by special arrangement only.

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1. Andrews, M. C.; Andrews, W. C., and Strauss, A. F.: Effects of Progestin-Induced Pseudopregnancy on Endometriosis: Clinical and Microscopic Studies, Am. J. Obst. & Gynec. 78:776 (Oct.) 1959.
2. Kistner, R. W.: Endometriosis and Infertility, Clin. Obst. & Gynec. 2:877 (Sept.) 1959.

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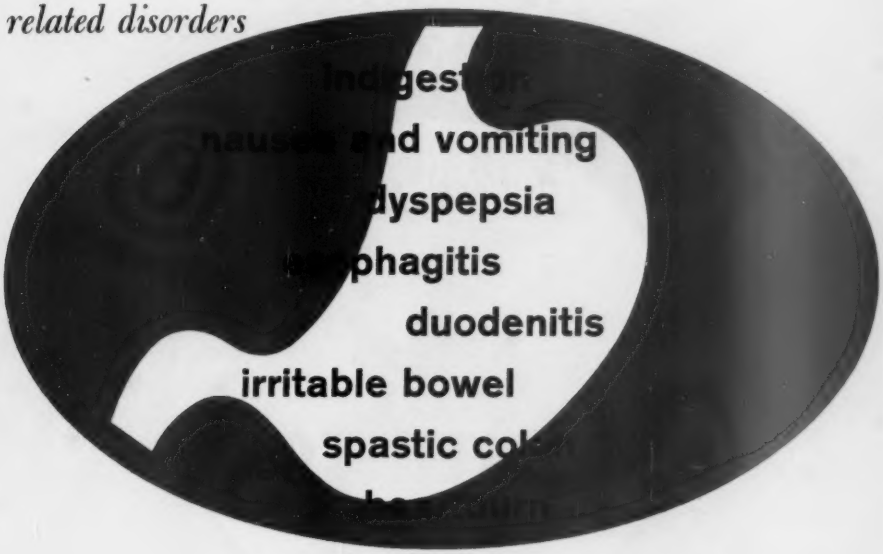
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Deutsch, E., and Christian, H.J.: J.A.M.A. 169:2012 *(April 25) 1959.*

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1. Biegeleisen, H. I.: Clin. Med. 2:1005, 1955. 2. Roberts, J. T.: Clin. Med. 4:1375, 1957. ©1960, A.P. Co.

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Bibliography: 1. Lamphier, T. A., and Lyman, F. L.: J. Internat. Coll. Surgeons 31:420-423 (April) 1959. 2. Smigel, J. O.; Lowe, K. J.: Hosp. P. H., and Gibson, J. H.: M. Times 86:1521-1526 (Dec.) 1958.

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25. Gordon, B.: Geriatrics *10*:397, 1955. 26. Gran, V. J., and Martinez, G. C.: Rev. Med. Chile 79:162, 1951. 27. Jaquet, P. F.: M. Ann. Dist. Columbia *21*:471, 1952. 28. Levine, E. R.: M. Rec. & Ann. *46*:332, 1952. 29. Lukas, D. S.: J. Allergy 22:411, 1951. 30. Miller, E. F.: New England J. Med. *251*:589, 1954. 31. Motley, H. L., and Tomashefski, J. F.: Arch. Ind. Hyg. Occup. Med. *5*:1, 1952. 32. Segal, M. S., and Attinger, E. O.: Am. J. Surg. *89*:387, 1955. 33. Segal, M. S.; Salomon, A.; Woods, C., and Herrchfus, J. A.: South. M. J. *47*:888, 1954. 34. Stuppy, G. W.: Am. Pract. Digest. Treat. *6*:72, 1955. 35. Tiffeneau, R.: Bull. Med. Paris *64*:199, 1950. 36. Watts, D. T., and Bragg, A. D.: J. Pharmacol. & Exper. Therap. *199*:2, 1957.

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2. Am. J. M. Sc. 230:357, Oct. 1955.
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4. J.A.M.A. 163:1482, April 20, 1957.

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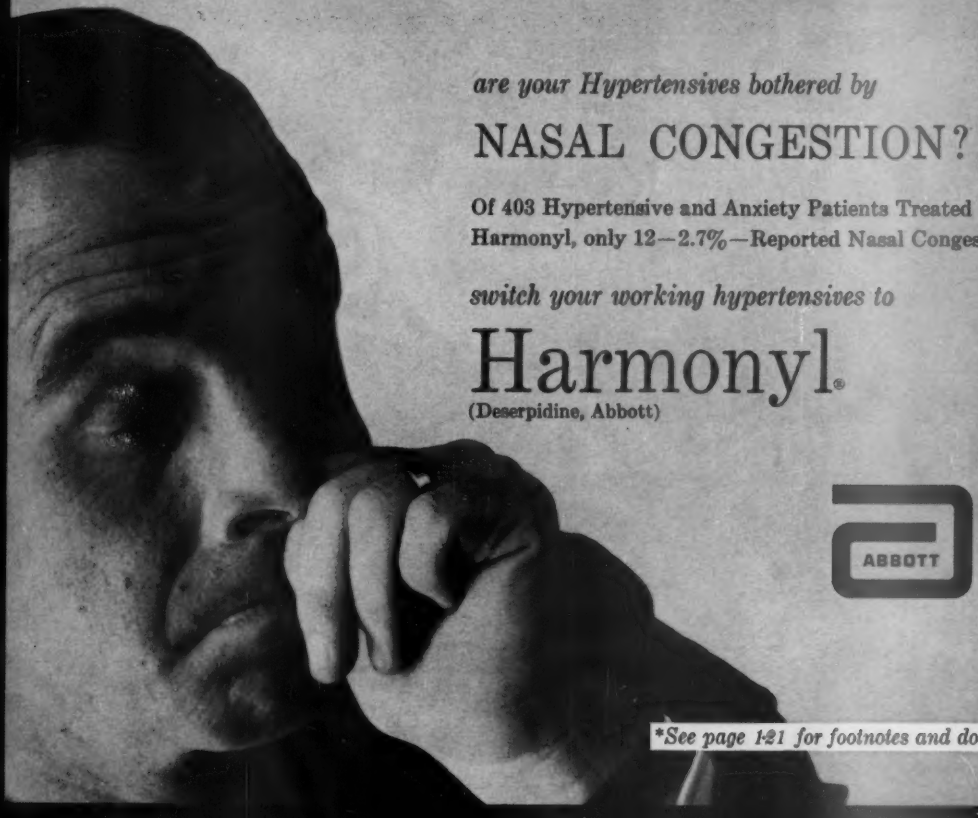
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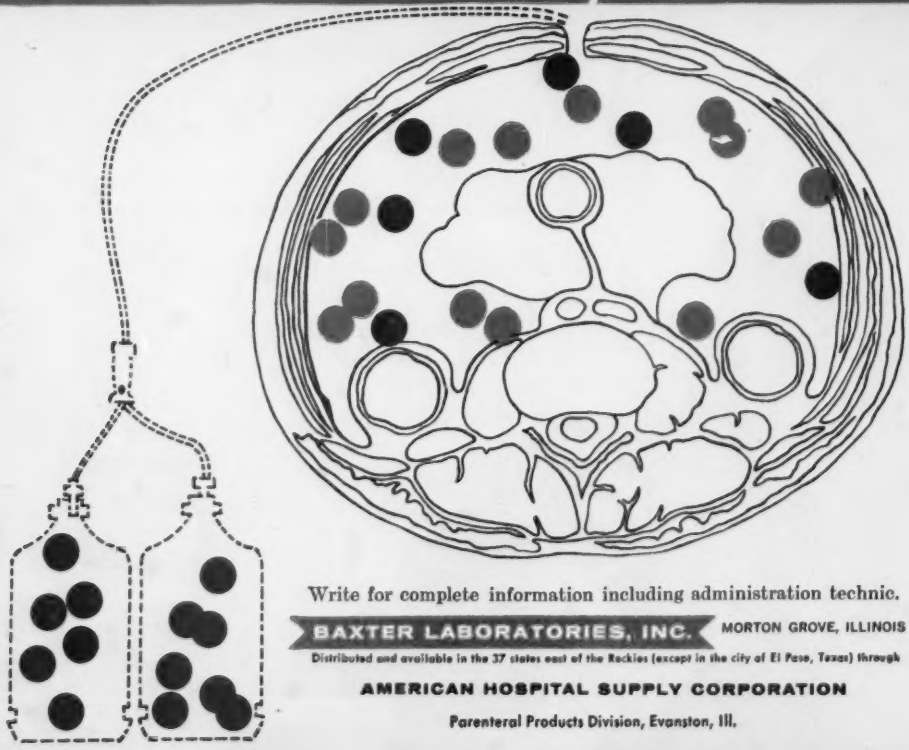
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Depression in Drug Treatment of Hypertension

Of 403 Hypertensive and Mixed Anxiety Patients Treated With Harmonyl, Only 6—1.5%—Reported Depression (mild)

Presented are notes from three clinical studies. Harmonyl was used as sole agent of therapy by 403 mixed hypertensives, and patients with mild functional/psychiatric disorders. Only six reported mild depression concurrent with therapy—an incidence of 1.5%.

Study #1. Two hundred and eighty-three patients treated in private practice, at hospital outpatient clinics, and in office psychiatric practice. Average initial dosage of Harmonyl was 0.1 mg. to 0.25 mg. three or four times daily. No patient received more than 6 mg. daily. Six reports of mild depression.[1]

Study #2. Eighty patients with benign essential hypertension were studied via "double-blind" method. Mean daily dosage of Harmonyl was 0.25 mg., with a minimum dosage of 0.1 mg. and a maximum of 0.5 mg. daily. No reports of depression.[2]

Study #3. Forty patients with hypertension and anxiety neurosis . . . from mild to moderately severe. Half of the group had received other antihypertensive agents at one time or another; these were discontinued before and throughout the study. Usual dosage of Harmonyl was 0.1 mg. three times daily after meals. Sometimes an additional dose was taken at bedtime. No reports of depression associated with this therapy.[3]

Other investigators have found so little indication of depression with Harmonyl therapy that they do not record it as a significant side-effect.

1. Billow, B.W. et al., The Use of a New Rauwolfia Derivative, Deserpidine, in Mild Functional Disturbances and Office Psychiatry, N.Y. J. Med., 59:1789, May, 1959.
2. Winsor, T., Comparative Effects of Various Rauwolfia Alkaloids in Hypertension, Diseases of the Chest, 35:415, April, 1959.
3. Rawls, W.B. and Evans, W.L. Jr., Clinical Experiences with Deserpidine in the Management of Hypertension and Anxiety Neurosis, N.Y. J. Med., 59:1774, May, 1959.

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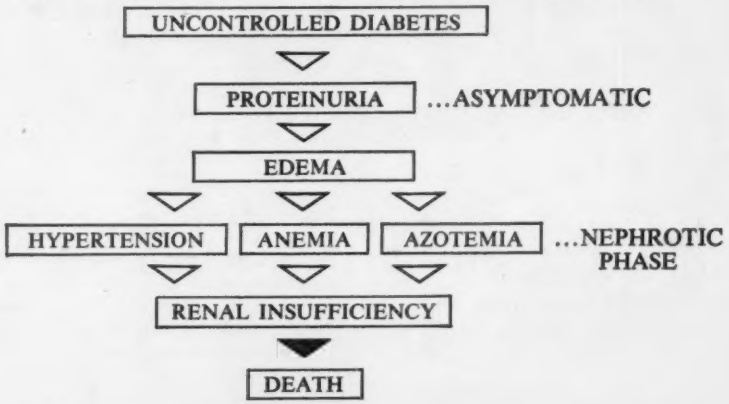
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Source: Whitehouse, F. W.: Postgrad. Med. *24*:54, 1958.

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1. Weiner, A. L.: Paper presented at the Conference on Recent Advances in the Treatment of Chronic Dermatoses, University of Cincinnati (Ohio), Nov. 5, 1959. 2. Compiled by the Medical Department, Eaton Laboratories, from case histories received. 3. Christenson, P. J., and Tracy, C. H.: Current Therapeutic Research 2:22, 1960. 4. Glas, W. W., and Britt, E. M.: Proceedings of the Detroit Symposium on Antibacterial Therapy, Michigan and Wayne County Academies of General Practice, Detroit, Sept. 12, 1959, p. 14. 5. Leming, B. H., Jr.: Ibid., p. 22. 6. Investigators' reports to the Medical Department, Eaton Laboratories.

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". . . our program has been one of polypharmacy in which we attempt to deplete body sodium with chlorothiazide. This drug is continued indefinitely as background medication for all antihypertensive drugs." Moyer, J. H.: Am. J. Cardiology, 3:199, (Feb.) 1959.



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in cirrhosis with ascites

"All three of the patients with Laennec's cirrhosis, ascites and edema had a favorable response, with a mean weight loss of 8 lbs., during the five-day treatment period with a slight decrease in edema." Castle, C. N., Conrad, J. K. and Hecht, H. H.: Arch. Int. Med., **103**:415, (March) 1959.



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"In a study of 10 patients with the nephrotic syndrome associated with various types of renal disease, orally administered chlorothiazide was a successful, and sometimes dramatic, diuretic agent." Burch, G. E. and White, M. A., Jr.: Arch. Int. Med., **103**:369, (March) 1959.

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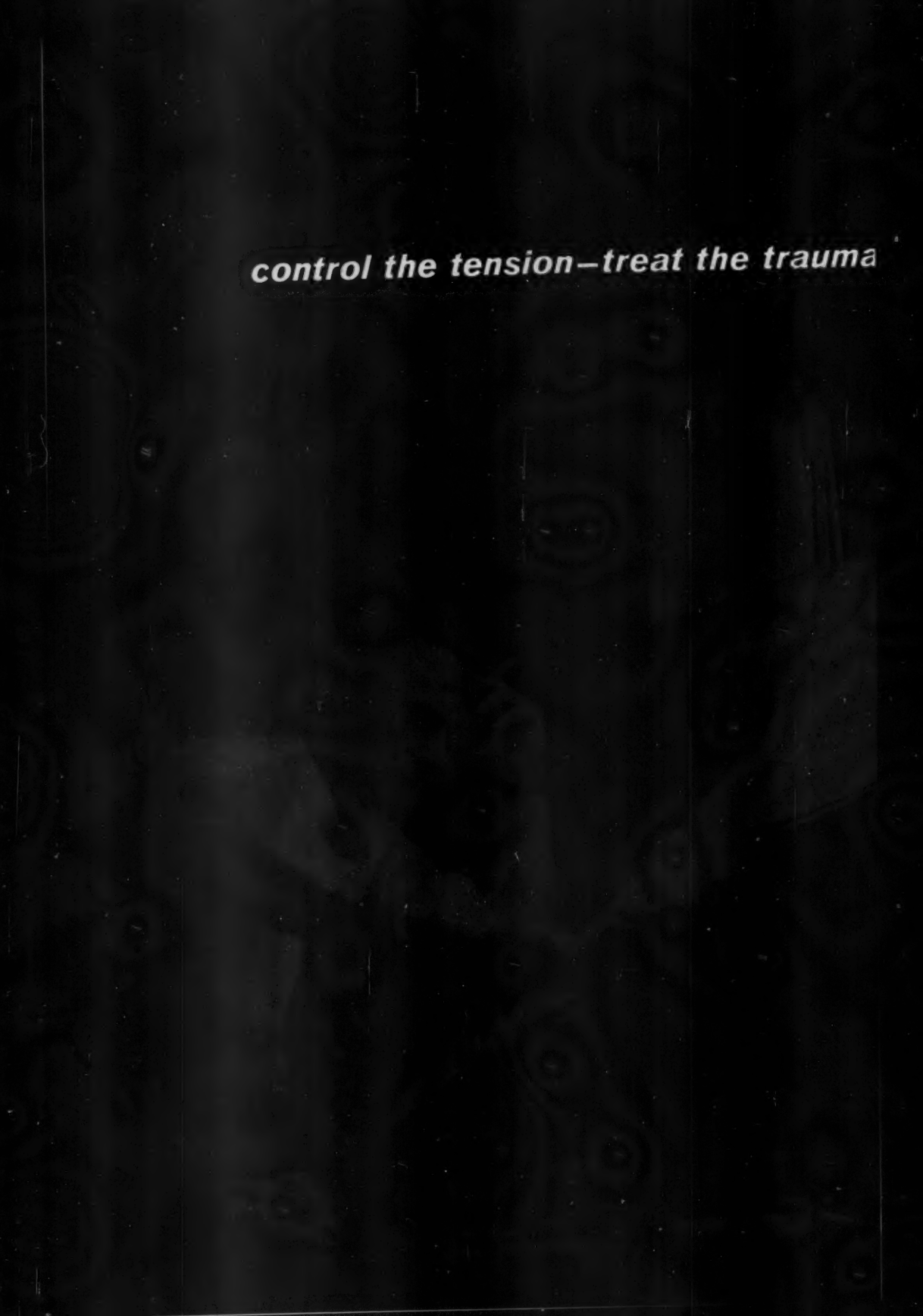
1. Knox, S.C.: The nervous system never rests, Scientific Exhibit. A.P.A., Philadelphia (April 27-30) 1959.

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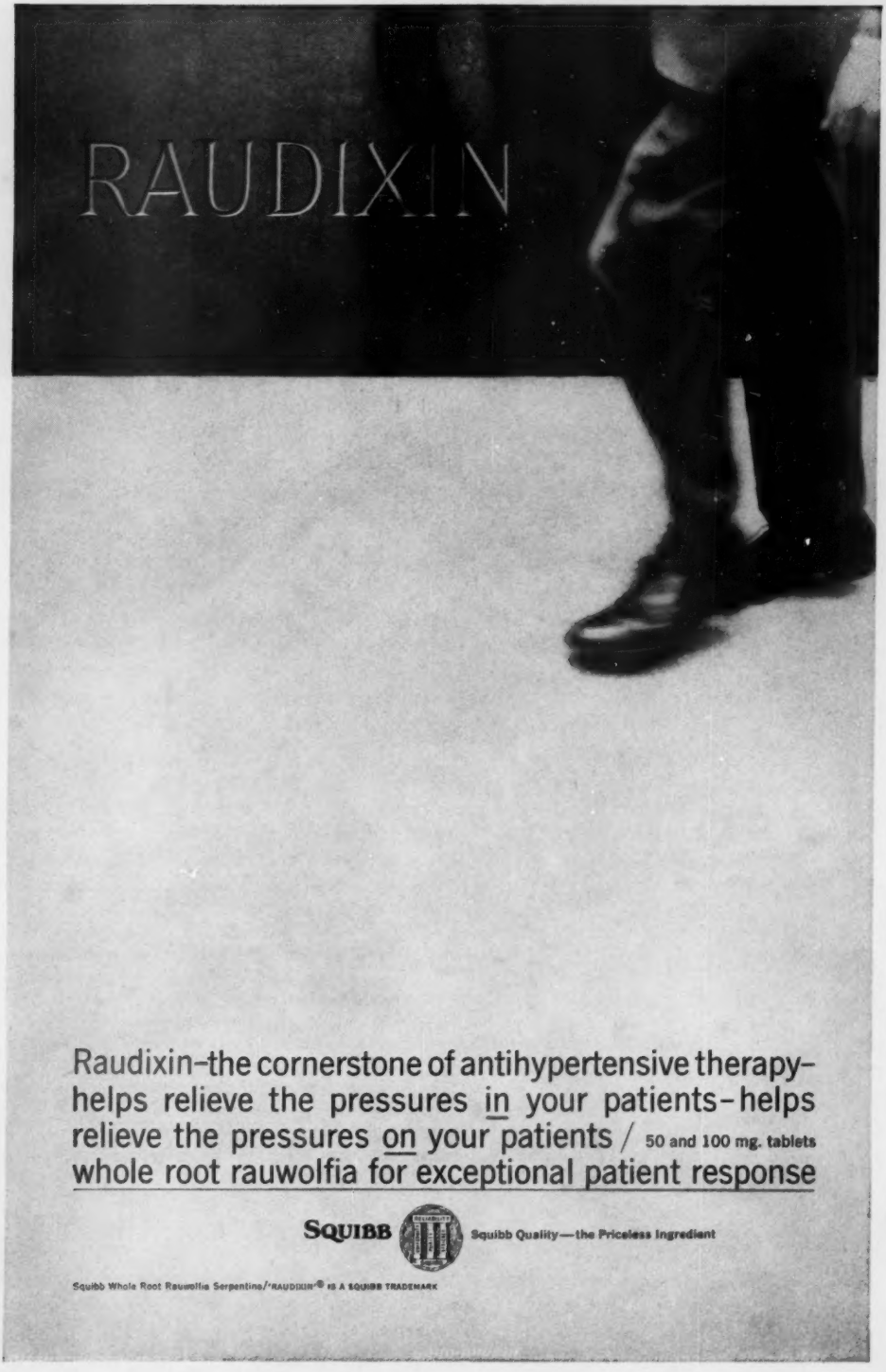
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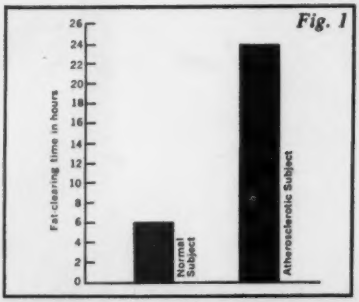
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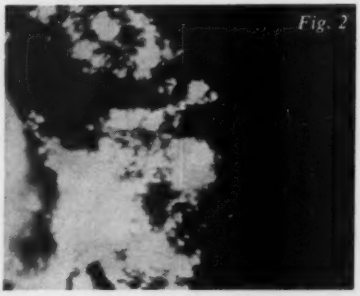
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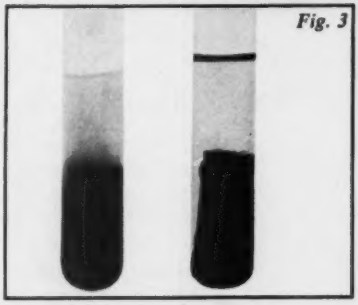
References: **1.** Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. **2.** Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. *7*:225 (Apr.) 1959. **3.** Stutman, L. J., and George, M.: Clin. Res. *7*:225 (Apr.) 1959. **4.** Wilkinson, C. F., Jr.: Annals of Int. Med. *45*:674 (Oct.) 1956. **5.** Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. *163*:727 (March 2) 1957. **6.** Fuller, H. L.: Angiology *9*:311 (Oct.) 1958. **7.** Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959. **8.** Fuller, H. L.: Circulation *20*:699 (Oct.) 1959.

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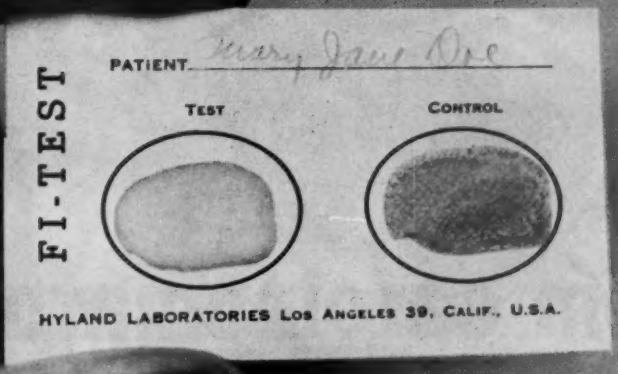
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In addition to the effectiveness required in challenging conditions, Tigan provides the safety which assumes special significance in everyday situations. Tigan shares the superior antiemetic potency (and mechanisms of action[5]) of the phenothiazines without entailing any of their risks or, for that matter, any of the side effects



to car sickness

safely controls the entire range of emetic situations without antihistamine side effects and without phenothiazine risks

of the antihistamines.[6-9] No sedation or other side effects were observed in TRAVEL SICKNESS patients, who were quickly and efficiently relieved by Tigan.[10] Nor was any drowsiness or other untoward reaction seen in 16 PREGNANT women, 15 of whom became asymptomatic on Tigan, while other antiemetic medication had failed or caused drowsiness in several.[10] In GASTROINTESTINAL vomiting, where results were "good" in 86 per cent and "fair" in 14 per cent, Tigan was "well tolerated" by all.[11]

TIGAN (COMPARED TO PLACEBO) IN SEASICKNESS

Medication	Number of Patients	RESULTS Improved	Unimproved
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Placebo, given initially	74	7	67
Tigan, given after failure of placebo	65	61	4

NO SPECIAL PRECAUTIONS OR CONTRAINDICATIONS—Patients on Tigan may drive an automobile or operate other mechanical equipment without the hazard of drowsiness; and carry on household activities without lethargy or sleepiness.

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For dosage instructions, consult product literature available on request.

References: 1. J. A. Lucinian and R. H. Bohn, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 2. O. W. Doyle, *Clin. Med.*, 7:43, 1960. 3. B. I. Shnider and L. Gold, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 4. D. W. Molander, *ibid.* 5. W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, *J. Pharmacol. & Exper. Therap.*, *126*:270, 1959. 6. Reports on file, Roche Laboratories. 7. O. C. Brandman, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 8. I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, *J. Newark Beth Israel Hosp.*, *9*:189, 1958. 9. W. B. Abrams, I. Roseff, J. Kaufman, L. Goldman and A. Bernstein, *New York J. Med.*, *59*:4217, 1959. 10. Personal communications. 11. L. McLaughlin, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959.

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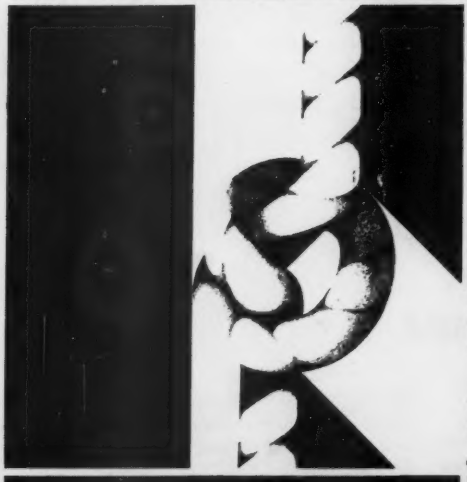
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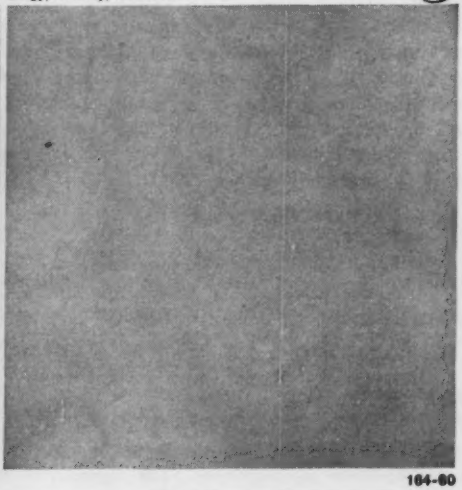
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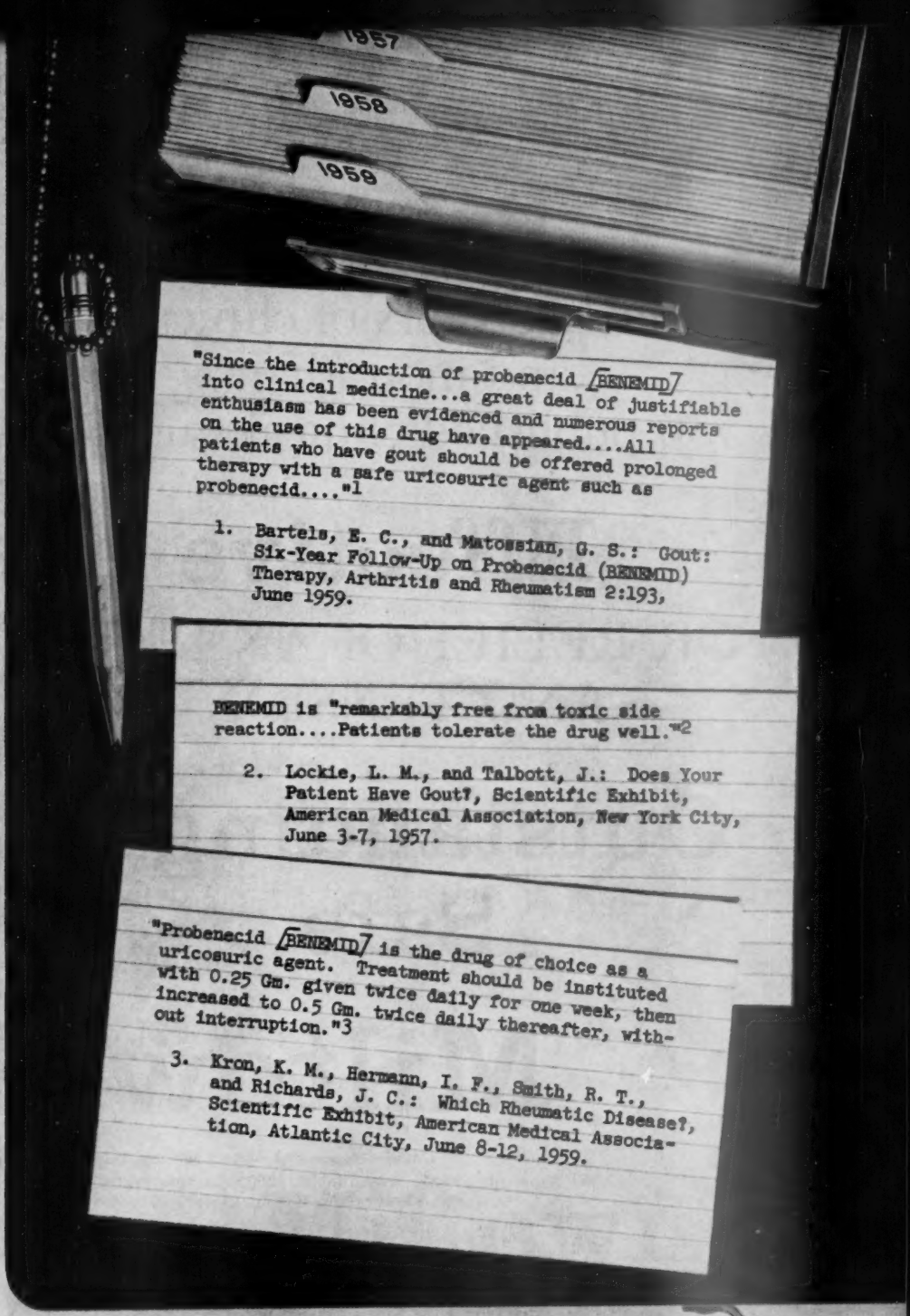
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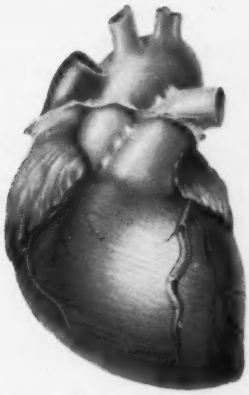
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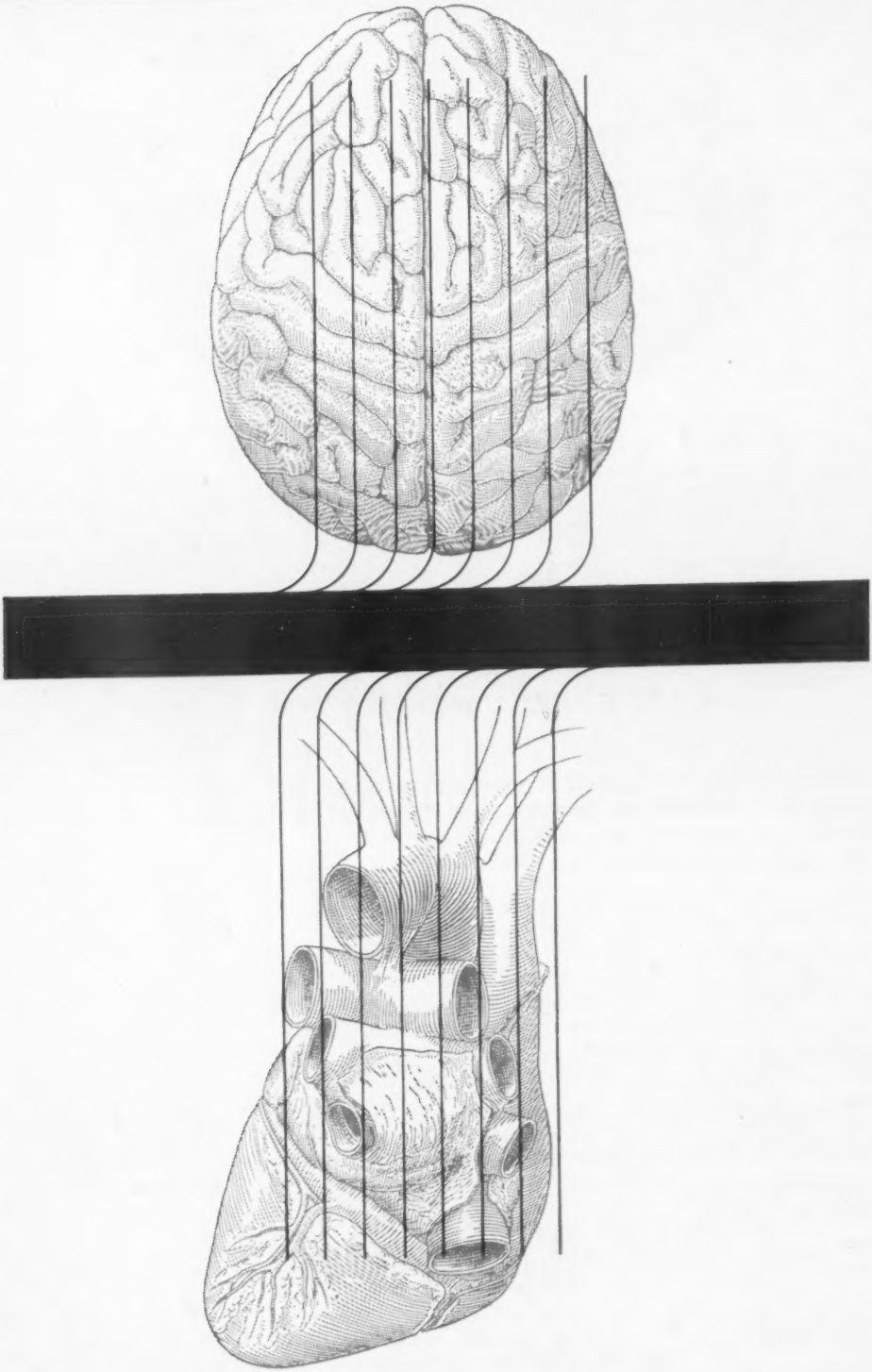
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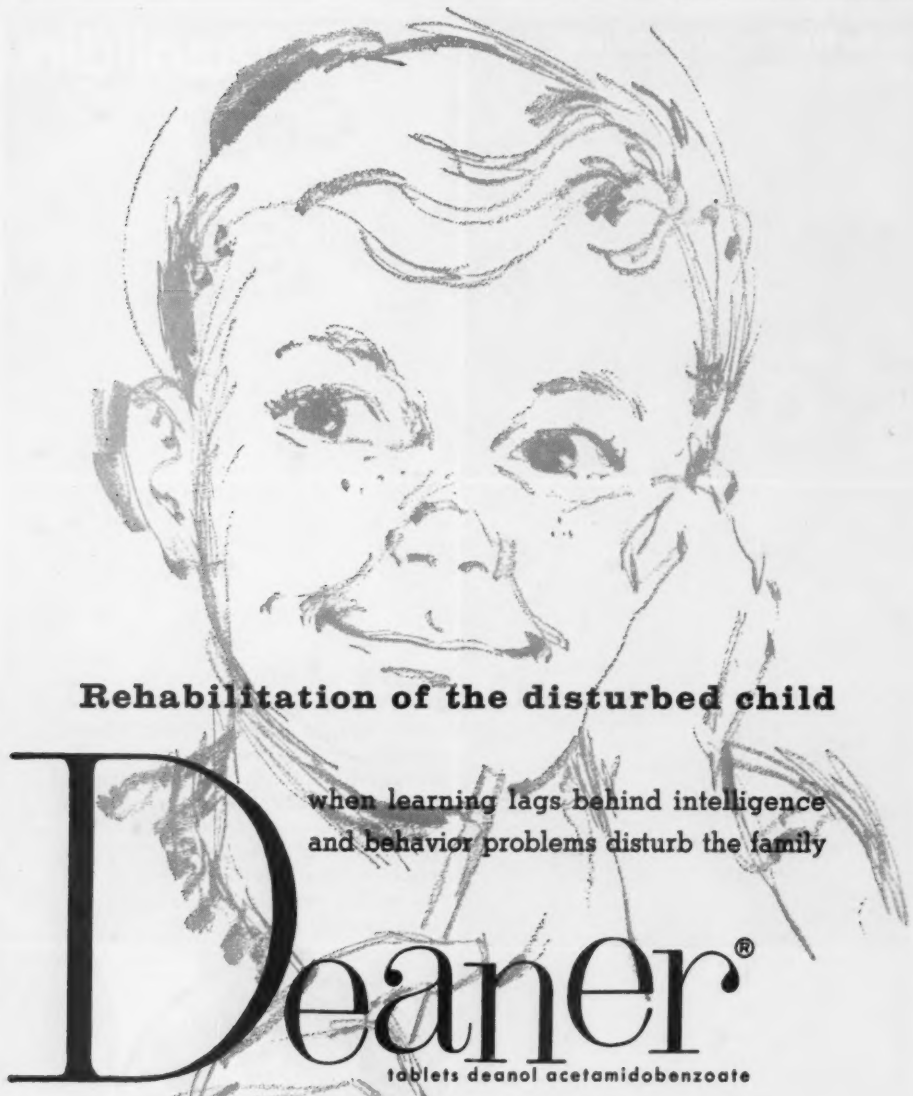
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